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DISEASES OF THE MOUTH

A Statistical Review of 4728 Patients

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THE following study of oral lesions comprises an additional group of patients seen in the past twelve years, combined with a previous report of a clinical and pathological study.[1]

In presenting this summary of 4728 patients with 5207 lesions we are able to give a more accurate idea of the frequency of oral lesions based on a compilation of both office and clinic cases. It was noted that no marked change has occurred in the incidence of the latter half of the period as compared with the first except for a rapid diminution in the number of cases of primary and secondary lesions of syphilis, and the increase in the local manifestations produced by contact of antibiotic preparations used locally in the oral cavity.

Psychosomatic influences in oral disease have been stressed in recent years, keeping pace with the dermatoses from psychologic causes. The psychosomatic factor in cheilitis exfoliativa, gingivitis, dental decay, aphthous stomatitis and recurrent herpes have all been noted by dermatologists and stomatologists in recent years.

Oral medicine, or stomatology, is a study confined to the curriculum of dental schools, relatively little organized instruction being given the medical student. Dental schools have recently stressed mucous-membrane lesions and the more recent graduates, on the basis of knowledge obtained from school instruction and as dental interns, are well qualified in their recognition. The dermatologists have also shown an increasing interest in the oral mucosa, especially since the advent of the newer drugs, such as the antibiotics, which tend to cause oral lesions by both local and endogenous action.

It has been twenty-five years since the course in oral medicine or oral diagnosis was instituted at Tufts College Dental School; in the period since then the study of disease in the oral cavity has broadened to include lesions other than purely dental conditions. Practically all the dental schools of the country today include the study of oral medicine or diagnosis as a part of the curriculum.

The courses of oral medicine taught in the various dental schools throughout the country are given by members of both the medical and dental schools. The medical profession is best represented by the dermatologists as teachers of oral disease; recently, members of the dental profession have increasingly assumed leadership in furthering research and teaching in oral disease.

A reduction in the incidence of gingival cases seen by us in recent years, both in the clinic and in office practice, seems to be directly related to the number of specialists in periodontology who are capable of handling their own gingival problems.

Since the mouth often reflects processes with etiologic factors elsewhere in the body it can well be considered the "diagnostic mirror" of the body.

To present an accurate incidence of oral lesions we have divided the cases seen in the office and clinic as they occurred in sequence. The former more nearly approach the actual incidence of oral lesions, for patients seek relief from disabilities, in contrast to the cases in the clinic, nonsymptomatic mucosal lesions being noted in the dental clinic by students and referred to the clinic in oral medicine for teaching purposes.

GINGIVAL LESIONS

The gums present lesions more often than any other structures in the oral cavity in both dentulous and edentulous cases. The lesions of people living under present conditions vary from mild gingival inflammatory processes, often focal in character, to the more severe hypertrophic changes, with evidence of infection. Our classification (Table 1) falls far short of dividing the various gum lesions as compared to the more comprehensive group of gingival lesions noted in recent publications in periodontology.[2] However, the simpler grouping of the gingival cases noted in our survey summarizes the cases seen in the office and clinic for practical pur-

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poses. It may be emphasized that the acute nonspecific and chronic marginal cases of gingivitis, together with other inflammatory enlargements, represent the bulk of gingival lesions. Attention is called to the small number of cases of Vincent's infection involving the gums diagnosed over a period of a quarter of a century as compared with other more numerous inflammatory lesions of the

TABLE 1. *Gingival Lesions.*

TYPE OF CASE	CASES SEEN IN OFFICE	CASES SEEN IN CLINIC	TOTALS
Chronic gingivitis	55	84	139
Gingivitis with hypertrophy	48	63	111
Marginal gingivitis	44	23	67
Chronic Vincent gingivitis	12	17	29
Acute Vincent gingivitis	27	21	48
Periodontoclasia	9	14	23
Hypertrophy of gingiva (edentulous)	18	14	32
Acute gingivitis	14	15	29
Mucous patches	7	8	15
Bismuth pigmentation	15	58	73
Gingivitis of pregnancy	3	1	4
Totals	252	318	570

gums. During World War I and for a short period thereafter the incidence of such infections was at its maximum. The period of World War II also showed a slightly higher incidence but far less than during World War I. Vincent's infection is based on a low resistance of the host, related to dietary deficiency and fatigue, and should be considered rare as demonstrated by accurate clinical and bacteriologic findings. The so-called chronic focal form is often associated with a hyperplastic focal gingival reaction, a rich flora of Vincent's organisms occurring

TABLE 2. *Classification of Cases of Stomatitis.*

TYPE OF CASE	CASES SEEN IN OFFICE	CASES SEEN IN CLINIC	TOTALS
Chronic aphthous stomatitis	139	46	185
Chronic stomatitis	45	45	90
Traumatic and contact stomatitis	41	83	124
Contact stomatitis (drug group)	32	15	47
Hypertrophic stomatitis (dentures)	28	6	34
Ulcerative stomatitis	19	26	45
Acute aphthous stomatitis	21	12	33
Chronic stomatitis (habit biting)	15	12	27
Xerostomia (dry mouth)	13	14	27
Gangrenous stomatitis (caused by bismuth)		1	1
Pyostomatitis vegetans	3	0	3
Totals	356	260	616

under the gingival tabs. This type of lesion is frequently prolonged by overtreatment from repeated medication with irritating chemical agents.

Pigmentary lesions of the gingiva due to bismuth have now practically disappeared, since bismuth is rarely used in the treatment of syphilis and has been confined to the treatment of certain dermatoses such as lupus erythematosus and lichen planus.

STOMATITIS

In classifying the various types of stomatitis (Table 2) one must consider the focal distribution of the inflammatory processes as well as the mouth as a whole. The focal areas of stomatitis are usually due to irritation from dentures, bridges and other local causes. A so-called stomatitis venenata caused by local irritants is rare as compared to skin reactions from local irritants. This may be explained on the basis of length of contact with the offending irritant, the natural resistance of the mucous membrane based on blood supply and local immunity to external irritants. Probably the most important explanation is that skin eruptions are produced by external irritants that are more frequently and constantly applied.

The incidence of the local effect of various dental appliances including artificial dentures is high in the clinic, which supplies most of these cases. Among the aged, especially women, irritation of the buccal mucosa is very common owing to lowered resistance from atrophy and diminution in the salivary outflow. We believe that galvanism, formerly discussed in the literature as an important cause of focal stomatologic lesions, should be eliminated in the absence of conclusive proof. It is no longer con-

TABLE 3. *Lesions of the Tongue.*

TYPE OF CASE	CASES SEEN IN OFFICE	CASES SEEN IN CLINIC	TOTALS
Papillitis	137	74	211
Glossitis areata migrans (geographic tongue)	80	59	139
Congenital fissured tongue	54	53	107
Chronic glossitis	48	49	97
Atrophic glossitis (anemia)	39	23	62
Atrophic glossitis (pernicious anemia)	7	5	12
Ulcerative glossitis	22	11	33
Glossodynia	12	8	20
Traumatic and contact glossitis	25	12	37
Syphilis of tongue:			
Chancre	2	2	4
Mucous patch	6	6	12
Gumma	4	2	6
Lingua lobulata	1	1	2
Atrophic syphilitic glossitis	27	46	73
Lingua nigra (hairy tongue)	22	15	37
False hairy tongue	5	6	11
Glossitis rhombic mediana	8	4	12
Tuberculosis of tongue	2	2	4
Macroglossia	1	1	2
Varicosities	5	12	17
Coated tongue (severe)	4	2	6
Totals	511	393	904

sidered good dentistry to remove various types of metallic fillings as potential causes of focal lesions. We have never accepted either the theory of galvanism as a cause of so-called "galvanic burns" of the buccal mucosa or the belief that these electrolytic discharges were a factor in the etiology of leukoplakia.

Hypertrophic lesions of the palate, the so-called mulberry palate often resulting from retention chambers in upper dentures, are decreasing.

LESIONS OF THE TONGUE

The tongue is more frequently involved than any other structure in the oral cavity (Table 3), minor sensory symptoms being based primarily on irritation of the highly specialized end organs, the

papillae, from frictional factors. The term papillitis is applied to symptoms of burning often caused by irritation of the fungiform papillae at the tip and the foliate papillae at the posterior lateral aspect of the tongue. The habit of rubbing the tongue against calculus deposit, involving the central and lateral lower incisors, is one of the commonest causes of burning tongue. It is desirable that all local conditions be explored before sensory symptoms of the tongue are attributed to endogenous factors.

Lingua nigra has shown an increase within the past few years; the use of the antibiotics has effected a change in the bacterial flora of the mouth, producing a black tongue, which is usually transitory. Yeast organisms are often demonstrated on smear and culture in these cases.

There has been a definite reduction in the number of cases of atrophic syphilitic glossitis. The improvement in early diagnosis of syphilis and the great decrease in the number of new cases, together with effective antibiotic treatment, should ultimately eliminate this precancerous lesion of the tongue.

The mechanism of development of the bald tongue of syphilis is of particular interest, for it reveals the sequence of pathological changes and the fact that the condition is irreversible. In syphilis the tongue is primarily infected with a rich dosage of treponemes, and in untreated or inadequately treated cases an endarteritis of both the large and the smaller blood vessels follows. As the condition progresses repair results in a sclerosing process, with gradual narrowing of the lumens of the blood vessels. The resulting atrophy of the papillae causes a smooth, bald tongue with a patchy distribution of the atrophic areas. Leukoplakia ultimately develops, especially if the patient is a smoker, because of the direct action of the products of combustion and heat on the smooth tongue, which has lost the protection of the filiform papillae. These plaques of hyperkeratotic epithelium tend to become malignant, resulting in single or multiple epidermoid carcinomatous lesions.

Lesions of the Lip

We have added to the numerical classifications of lip lesions and note an increasing number of cases of intertrigo labialis (Table 4). The edentulous aged persons in the United States now represent a large percentage of the population. One of the commonest causes of intertriginous maceration at the external commissures of the lips is the widespread use of artificial dentures. The resulting atrophy of the gingival and alveolar process from the protracted wearing of these dentures results in a "closing of the bite," with the complications of flaccidity of the commissures and drooling of saliva, producing the characteristic lesions of intertrigo labialis. A change in the mechanics induced by relining the dentures or the wearing of new plates thus "opening the bite" should promptly clear up this condition. Intertriginous maceration of the lips is rarely caused by avitaminosis, and in all cases of this condition dental consultation is desirable.

Lipstick as a cause of contact cheilitis may be considered as negligible when one considers the extent of its routine use, indicating that this type of cosmetic is chemically inert. Sun exposure frequently results in acute cheilitis with vesiculation and sensitivity to the sun's rays that become so marked that the slightest exposure causes exacerbations.

Table 4. *Lesions of the Lip.*

Type of Case	Cases Seen in Office	Cases Seen in Clinic	Totals
Chronic cheilitis	45	25	70
Intertrigo labialis	38	35	73
Cheilitis exfoliativa	27	13	40
Cheilitis glandularis	14	12	26
Cheilitis venenata	18	6	24
Fissure of lip	14	9	23
Chronic lymphangitis	9	3	12
Acute lymphangitis	1	1	2
Chancre of lip	2	3	5
Dilated vein	15	2	17
Melanosis	2	0	2
Nevus pigmentosus	2	1	3
Traumatic ulcer	1	2	3
Granuloma pyogenicum	3	0	3
Totals	191	112	303

Table 5. *Neoplasms and Cysts.*

Type of Case	Cases Seen in Office	Cases Seen in Clinic	Totals
Neoplasms:			
Epidermoid carcinoma:			
Lip	64	36	100
Tongue	32	22	54
Buccal mucosa	22	24	46
Floor of mouth	18	10	28
Gingiva	16	12	28
Palate	6	6	12
Totals	158	110	268
Epulides:			
Fibrous	40	27	67
Granulomatous	30	17	47
Giant-cell	8	4	12
Totals	78	48	126
Acanthoma	12	12	24
Fibroma:			
Tongue	32	23	55
Buccal mucosa	28	16	44
Lip	9	13	22
Palate	11	11	22
Gingivae	12	7	19
Totals	92	70	162
Hemangioma	19	17	36
Lymphangioma	4	1	5
Granuloma and granuloma fissuratum	48	12	60
Papilloma	23	8	31
Mixed tumor	4	1	5
Fibroangioma	2	1	3
Osteoma	1	2	3
Lymphoma	1	0	1
Adamantinoma	1	1	2
Totals	103	43	146
Cysts:			
Ranula	28	28	56
Mucous cysts:			
Tongue	9	8	17
Lip	75	48	123
Buccal mucosa	19	15	34
Totals	103	71	174

Neoplasms and Cysts

This group represents the largest in this summary (Table 5). A sufficient number of malignant lesions of the oral cavity and lips — namely, 268 cases —

gives interesting information about sex incidence and location. Ten per cent of the oral cancers occurred in women, usually in the later decades of life. This percentage confirms the generally accepted incidence in the sexes. Many of the cases of carcinoma in aged women are found in edentulous mouths, being due to irritation of faulty-fitting dentures with frequent involvement of the tongue. Neoplasms in the oral cavity, according to a statistical study of our cases, are of the epidermoid type, representing almost 100 per cent of the cases of cancer. Our findings conform to statistics in the recent medical literature.[3]

Oral Eruptions Due to Dermatoses, Viruses and Drugs

The dermatoses with eruptive manifestation in the oral cavity (Table 6) comprise only 5 per cent of the lesions noted in our survey, and the virus infections with the drug group combined account for another 2 per cent of the total. Because the many patients with herpes simplex labialis require no medical attention a large group of virus infections are necessarily not included in the statistical study.

Table 6. *Virus and Drug Dermatoses.*

Type of Case	Cases Seen in Office	Cases Seen in Clinic	Totals
Dermatosis:			
Lichen planus — oral	42	26	68
Lichen planus bullosa (oral)	2	2	4
Lichen planus (oral and skin)	7	18	25
Pemphigus vulgaris and vegetans (oral lesions)	7	7	14
Oral pemphigus	6	4	10
Benign mucous-membrane pemphigus	3	1	4
Angioneurotic edema	12	5	17
Lupus erythematosus	18	19	37
Erythema multiforme	22	15	37
Xanthomatosis	1	1	2
Lupus vulgaris		1	1
Scleroderma		1	1
Totals	120	100	220
Virus:			
Herpes simplex labialis, recurrent	26	10	36
Herpes simplex labialis	14	16	30
Herpes buccalis, recurrent	7	4	11
Acute infectious gingivostomatitis	11	4	15
Herpangina (Coxsackie virus)	2	0	2
Verruca vulgaris	11	2	13
Molluscum contagiosa	1	0	1
Totals	72	36	108
Drug:			
Phenophthalein	2	3	5
Barbiturates	3	3	6
Dilantin	3	5	8
Potassium iodide	1	0	1
Sulfonamides	3	2	5
Penicillin	3	2	5
Chlortetracycline	3	1	4
Quinacrine	1	0	1
Totals	19	16	35

Lichen planus, with involvement both of the mouth alone and of the skin and the mouth, accounts for the largest number of dermatoses (Fig. 1 and 2). The cases of pemphigus with oral lesions are next in frequency and with lichen planus account for 50 per cent of all the cases. The benign mucous-membrane pemphigus is rare; the lesions involve the gums and persist over a period of years.

Silent lesions of lupus erythematosus in the oral cavity are relatively numerous and the incidence is definitely higher than is usually assumed, since the mouth is not examined in all cases. The vesicular and bullous dermatoses in the oral cavity, together with virus and drug eruptions, present problems that challenge the diagnostic skill of those interested in oral disease.

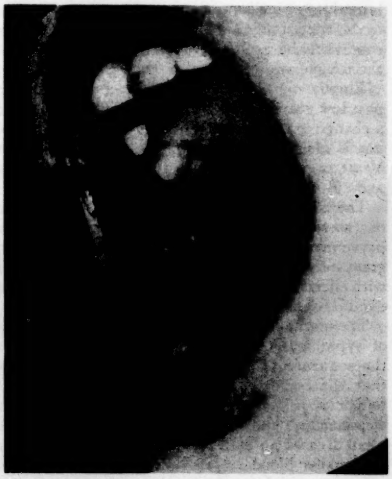

Figure 1. *Typical Appearance of Lichen Planus Bullosa of the Oral Cavity.*
Note the bullous lesion on the buccal mucosa.

The more recent successful isolation of the virus of herpes simplex by cytologic and cultural methods accounts for an apparent increase in the incidence of these lesions. Acute infectious herpetic gingivostomatitis can now be definitely diagnosed, and although most of the cases occur in infancy and childhood many cases have appeared in adults. Herpangina due to the Coxsackie virus, a relatively mild disease occurring in epidemic form in children, is easily recognized clinically by the localization of the lesions in the soft palate and uvula.

Cases of stomatitis medicamentosa caused by the antibiotics have shown an increase, with a corresponding reduction in the incidence of oral eruptions from the use of sulfonamides. The local use of antibiotic preparations in the oral cavity produces a large number of reactions, the most common being a diffuse erythema and edema of the buccal mucosa, with a denudation of the coating of the tongue and prominence of the filiform papillae. The reactions are usually minor, but a severe type of necrotic

lesions occasionally occurs in susceptible persons. Changes in the bacterial flora, with a relative increase in the yeast organisms, often cause a grayish to black pigmentation of the coating of the tongue of a transitory nature.

FIGURE 2. *Lichen Planus of the Buccal Mucosa, Showing Severe Acanthosis with Infiltrate in the Tunica Propria.*

LEUKOPLAKIA

The numerous cases of leukoplakia (Table 7) indicate that these precancerous lesions account for about 15 per cent of all the cases observed both in the office and in the clinic. The typical histologic appearance with early epidermoid carcinoma is shown in Figure 3. This large group amplifies a previous report of 316 cases[4] and supports the idea of the frequency of this precancerous lesion. An important factor seems to be the products of combustion, particularly in pipe smokers, on susceptible mucous membrane in older persons and is probably related to hormonal inactivity. A characteristic lesion is demonstrated in Figure 4.

TABLE 7. *Leukoplakia.*

TYPE OF CASE	CASES SEEN IN OFFICE	CASES SEEN IN CLINIC	TOTALS
Tongue	70	96	166
Lip and commissures	78	63	141
Buccal mucosa	117	83	200
Gingiva	43	52	95
Palate	41	28	69
Totals	349	322	671

FIGURE 3. *Leukoplakia, with Early Epidermoid Carcinoma. Note the irregularity of the basal layer, with beginning invasion of the tunica propria.*

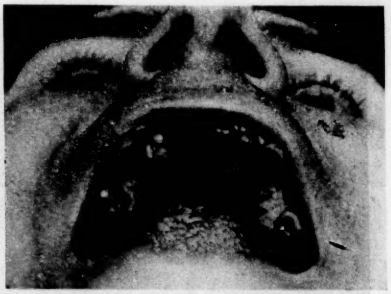

FIGURE 4. *Leukoplakia of the Palate (Smoker's Palate), Showing the Typical Leathery Consistence, with Umbilication of the Mucous Glands.*

BLOOD DYSCRASIAS, CONSTITUTIONAL DISEASE AND AVITAMINOSIS

Atrophy of the papillae, producing a reversible type of smooth tongue often associated with anemia and avitaminosis (Table 8), represents the commonest lesion of the tongue in the series. In pernicious anemia, now controlled by proper therapy, one rarely sees the advanced atrophic glossitis occurring before the use of liver and folic acid. Bleeding gums, in the absence of local causes of irritation, suggest an underlying blood dyscrasia such as agranulocytosis, aplastic and hemolytic anemia or an acute form of leukemia.

Avitaminosis as a cause of oral lesions has been overemphasized in the medical literature, especially

TABLE 8. *Blood Dyscrasias, Avitaminosis and Constitutional Diseases.*

TYPE OF CASE	CASES SEEN IN OFFICE	CASES SEEN IN CLINIC	TOTALS
Atrophic glossitis (secondary anemia)	36	22	58
Atrophic glossitis (pernicious anemia)	7	5	12
Acute gingivitis (aplastic anemia)	2	1	3
Hypertrophic gingivitis (monocytic leukemia)	2	1	3
Hypertrophic gingivitis (chronic myeloid leukemia)	1	1	2
Hemophilia	2	0	2
Tuberculosis of tongue and buccal mucosa	4	2	6
Tuberculosis cutis orificialis	1	0	1
Purpura hemorrhagica	3	5	8
Gingivitis (diabetes)	1	2	3
Pellagra	4	3	7
Chronic atrophic glossitis (avitaminosis)	0	2	2
Magenta tongue	0	2	2
Totals	63	46	109

pharmaceutical literature with colored plates. In New England it is extremely rare to find a classic case of oral disease from vitamin deficiency. Oral lesions of pellagra are occasionally noted in alcoholic patients with associated niacin deficiency. Intertriginous lesions at the external commissures of the lips are, in practically all cases, due to poorly fitting

FIGURE 5. *Syphilitic Glossitis, Showing the Atrophic Surface, with Leukoplakia.*

artificial dentures and not to avitaminosis. Owing to early use of penicillin therapy syphilitic oral lesions in the secondary stage are rare. Only the atrophic glossitis of syphilitic origin (Fig. 5) demonstrated in elderly patients is still seen in practice.

TABLE 9. *Miscellaneous Lesions.*

TYPE OF CASE	CASES SEEN IN OFFICE	CASES SEEN IN CLINIC	TOTALS
Fordyce's disease	25	60	85
Neuralgia	23	60	83
Torus palatinus	13	12	25
Exostoses	10	11	21
Alveolar abscess	12	6	18
Parotitis, including ducts	6	7	13
Syndromes:			
Plummer-Vinson	4	0	—
Stevens-Johnson	3	0	—
Costen	2	1	10
Tic douloureux	3	6	9
Abscess, oral	4	5	9
Calculi, salivary ducts	3	4	7
Cervical-lymph-node adenitis	2	6	8
Cleft palate	5	1	6
Vincent's infection (tonsil)	3	2	5
Hutchinsonian teeth	3	0	3
Absence of enamel	1	2	3
Mottled enamel	2	0	2
Osteomyelitis of jaw	2	1	3
Alae gingivae	2	1	3
Moniliasis	3	0	3
Bell's paralysis	1	1	2
Congenital ectodermal defect	2	0	2
Chancre, tonsil	1	0	1
Chancre, buccal mucosa	1	0	1
Argyria	1	0	1
Paget's disease	1	0	1
Totals	138	186	324

MISCELLANEOUS LESIONS

The condition known as Fordyce's disease involving the lips and buccal mucosa is an extremely common finding in adults. The 85 cases enumerated refer to a group of pronounced cases of Fordyce's granules, excluding mild types. Only the pronounced cases of torus palatinus are recorded, and the incidence of mild forms of palatal exostoses is much higher among the general population.

PSYCHOSOMATIC GROUP

We have classified in this group the cancerphobia often seen both with and without tangible lesions. The ratio of cancerphobia in females and males is 10:1, and that of cancer is just the reverse. Although a large number of cases of papillitis are caused by frictional irritation, we have not included this group among the psychosomatic cases. It was suggested that some cases of cheilitis exfoliativa are psychosomatic in origin. In 40 cases of this condition we are satisfied that at least 6 were from emotional causes.

TABLE 10. *Psychosomatic Group.*

TYPE OF CASE	CASES SEEN IN OFFICE	CASES SEEN IN CLINIC	TOTALS
Cancerphobia	145	71	216
Psychosomatic, with lesions	25	12	37
Psychosomatic, without lesions	16	11	27
Habit biting	15	12	27
Ptyalism	9	6	15
Syphilophobia	2	0	2
Totals	212	112	324

SUMMARY AND CONCLUSIONS

A statistical study of 4728 patients with 5207 oral lesions is presented.

An increase in the incidence of cases of contact stomatitis is noted in the past decade owing to the local use of antibiotics. An ever-increasing incidence of psychosomatic cases is noted.

Periodontology, a relatively new specialty in dentistry has clarified the etiologic factors in many gingival diseases.

The differentiation of vesicular and bullous eruption in the oral cavity offers a challenge in the diagnosis.

Leukoplakia buccalis is the most common single important lesion in the oral cavity.

Except for a residual group of syphilitic atrophic glossitis the incidence of syphilitic lesions in the oral cavity has diminished with the rapid lowering of the morbidity of this disease.

REFERENCES

1. McCarthy, F. P. Clinical and pathologic study of oral disease based on 2,300 consecutive cases. *J. A. M. A.* 116:16-21, 1941.
2. Glickman, I. *Clinical Periodontology: The periodontium in health and disease, recognition, diagnosis, and treatment of periodontal disease in the practice of general dentistry.* 1019 pp. Philadelphia: Saunders, 1953.
3. Lane, S. L. Oral cancer. *Oral Surg.* 6:258-267, 1953.
4. McCarthy, F. P. Etiology, pathology and treatment of leukoplakia buccalis, with report of 316 cases. *Arch. Dermat. & Syph.* 34: 612-623, 1936.

GASTRIC ULCER*

A Study of 138 Patients

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GASTRIC ulcer was mentioned during the eighteenth century but was not recognized as a definite pathologic entity until Cruveilhier's[1] classic description of chronic simple ulcer of the stomach in 1829. In 1857 Brinton[2] discussed the difficulty of differentiating benign from malignant gastric ulcers, and pathologists at the Mayo Clinic, in the beginning of the twentieth century, showed that many of the lesions that appeared benign were actually malignant. Recently, other authors have reported a high incidence of cancers in cases of gastric ulcer, but some of these studies have included obvious carcinomas.

Cases of long-standing or recurring gastric ulcers that ultimately developed into carcinoma have been described, suggesting the possibility of malignant metamorphosis of benign gastric ulcer. Morley[3] and others, however, have asserted that malignant change in a gastric ulcer is infrequent, occurring in not more than 1 or 2 per cent of cases.

Probably the most important problem in gastric ulcer, therefore, is the occurrence of carcinoma. Welch and Allen,[4] Ravdin and Horn[5] and others have supported the concept that with few exceptions these patients should be operated on promptly for assurance against cancer — in fact, Ochsner and Blalock[6] and Lahey[7] have stated that all these patients should be treated surgically. Some investigators, however, believe that their studies justify a more conservative attitude and that a higher proportion of patients should receive a trial with medical therapy. Smith and Jordan,[8] in reporting a study of 600 cases, concluded that gastric ulcer is not so perilous that the patient cannot be treated individually rather than by a general policy of resection.

It is the purpose of this paper to present the observations and conclusions in a study of 138 patients with gastric ulcer treated at the Veterans Administration Hospital in Louisville, Kentucky.

Method of Study

During the five-year period from April 15, 1946, to April 15, 1951, we studied our patients with gastric ulcer in an effort to determine the best criteria for selecting cases in which early surgical operation was indicated. We were particularly interested in the problem of differentiating benign from malignant ulcers. Certain criteria were tentatively set up for this purpose by means of x-ray examination, aided in some cases by gastroscopic study. Also, we were influenced by the clinical aspects of the case and laboratory data.

Radiologically, the only diagnostic criterion of a gastric ulcer was the demonstration of the niche itself. An ulcer was suspected of being malignant when its niche was superimposed on a filling defect within the normal boundary of the gastric lumen, if the gastric rugae in the region of the ulcer were effaced (because of infiltration) or if the contour of the gastric wall adjacent to the niche showed a persistent irregularity or had a ragged appearance.

Other factors considered suggestive of cancer included the existence of a large ulcer (2.5 cm. or more in diameter), the presence of achlorhydria or hypochlorhydria, a reliable history of recurrence or refractoriness to medical management, the recent development or rapid progression of symptoms in a patient more than fifty years of age and a marked loss of weight. All ulcers on the greater curvature were presumed to be malignant; otherwise, location was not in itself considered significant. When an active ulcer was demonstrated in the duodenum, as well as in the stomach, it was believed that if none of the findings listed above were present, there was a little more assurance that the gastric lesion was likely to be benign.

In general we were greatly influenced by the x-ray interpretation. If the radiologist considered for any reason that the lesion was malignant the condition was regarded as surgical. On the other hand if he found nothing suggestive of carcinoma and there were no other indications the patient was placed on medical treatment, which was continued until the ulcer was completely healed. If it did not heal or was not healing rapidly enough after two to four weeks to justify continued observation under medical management, or if there was a recurrence after healing, surgical intervention was considered necessary.

After discharge from the hospital, we arranged to follow with x-ray examinations all patients whose lesions had not been positively identified by surgical resection, at intervals of two or three months during the first year and three to six months thereafter.

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Results

During the five-year period of this study 138 patients were treated for gastric ulcer, representing 151 total admissions for separate and distinct ulcerative lesions; 162 gastric ulcers were treated, since some patients had multiple ulcers. The total number of admissions to the hospital during this period was 42,276. This gives an incidence of 0.35 per cent, or approximately 3 cases per 1000 admissions.

Nine cases of ulceration of the stomach were omitted from this series because a diagnosis of cancer had been made on the initial x-ray examination, and hence they presented no diagnostic or management problem. Accordingly, our study has evolved to a great extent into a determination of the incidence of carcinoma in gastric ulcers that appeared to be benign and into an evaluation of criteria of malignant degeneration in this type of case.

As shown below, there were 3 cases of proved carcinoma and 1 that is assumed to have been malignant on the basis of the family physician's clinical diagnosis. In addition, 6 of 16 patients with recurrent ulcers refused surgery, and the incidence of carcinoma in this group is problematic.

Diagnosis

Of the 151 admissions for gastric ulcer, the diagnosis was made by x-ray examination in 135, by operation (emergency cases of hemorrhage or perforation) in 10, by autopsy in 5 cases and by gastroscopic examination alone in 1.

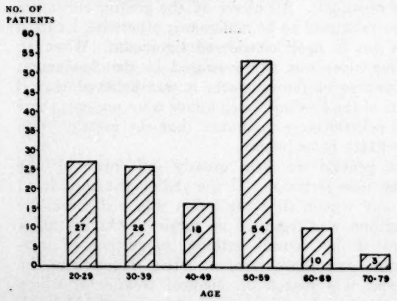

FIGURE 1. *Numbers of Patients with Gastric Ulcer in Various Age Groups.*

Of these patients 10 had multiple gastric ulcers, 9 having had two each and 1 having had three.

Gastroscopic examination was performed on 11 patients. In 1 case the diagnosis was made entirely by this means. The lesion in this case was on the posterior wall and was not visualized on x-ray study. To the limited extent that gastroscopic examinations were performed in this study, they did not prove to be particularly helpful either in demonstrating the ulcers or in indicating their benign or malignant character.

The features on x-ray examination used for differentiating benign from malignant lesions proved to be reliable in their broader usage, but our studies indicate that they are of limited value in estimating the probability of carcinoma in ulcers that appear to be benign.

Sex

Of the 138 patients 137 were men, and 1 was a woman. This is accounted for in part by the fact that less than 1 per cent of the patients admitted to this hospital are women.

Age

The age incidence of the ulcers is shown in Figure 1. It will be noted that the preponderance of cases occurred in the groups from twenty to forty and fifty to sixty years of age. This may be explained partly by the fact that in a Veterans Administration hospital the patients tend to fall into these two age groups because of World Wars I and II.

All 3 of the proved carcinomas were in patients past fifty years of age. This is in accordance with the findings of other investigators, who have reported a higher incidence of carcinoma in the older age group.

Duration

Twenty-two per cent of the patients had had symptoms for less than a year, 54 per cent for less than five years, 22 per cent for five to ten years and 24 per cent for more than ten years (including 9 per cent who had had symptoms, intermittently, for more than twenty years).

TABLE 1. *Relative Frequency of Symptoms.*

	Symptoms in Order of Frequency Mentioned	No. of Patients	Percentage of Patients
1.	Epigastric pain between meals	115	83.4
2.	Nausea	88	63.7
3.	Vomiting	87	63.0
4.	Weight loss	83	60.0
5.	Pain relieved by food or alkali	68	49.0
6.	History of vomiting blood or "coffee grounds"	36	26.1
7.	History of tarry stools or passing blood per rectum	33	23.9
8.	Gaseous distention or epigastric fullness	20	14.5
9.	Nocturnal pain	16	11.6
10.	Anorexia	14	10.3
11.	Other abdominal pain	10	7.2
12.	Nervousness	6	4.3
13.	Constipation	6	4.3
14.	Vague indigestion	4	2.9
15.	Weakness	4	2.9
16.	Hiccups	1	0.7

Symptoms

One hundred and thirty-seven patients had gastrointestinal symptoms. In only 1 was the ulcer found incidentally. The incidence of symptoms is shown in Table 1. An analysis of the type and duration

of the gastrointestinal symptoms showed them to be so variable, that they are not considered to have been of any appreciable diagnostic significance.

Loss of Weight

As indicated by actual weight determinations approximately 50 per cent of the patients had lost more than 10 pounds. Approximately 25 per cent had lost more than 20 pounds, and 25 per cent had lost no weight at all. It is evident that the amount of weight loss in the patients in this series was quite variable, corroborating the findings of others that a significant percentage of patients with benign gastric ulcer may have a marked loss of weight.

Gastric Analysis

Gastric analyses were performed on 94 patients. Of these, 33 per cent had no free hydrochloric acid; 60 per cent had less than 20° and 75 per cent less than 30° on the fasting specimen. Only 5 of the 31 patients with no free acid on the fasting specimen had histamine achlorhydria. In these cases neither the dosage of histamine nor the interval for taking specimens was standardized, and we are unable to say definitely that they represent absolute histamine achlorhydria.

Gastric analyses in the patients of this series showed a trend to low acidity on the fasting specimen. This is in accordance with the findings of Levin et al.,[9] who have shown that in patients with benign gastric ulcer the average output of acid under basal conditions is less than that found in normal persons.

Location of Ulcers

The location of the ulcers is shown in Table 2. The absence of cases of cancer in the 33 ulcers in the pyloric canal is consistent with the findings of others, who have reported a comparatively lower incidence of carcinoma in this area. In fact some investigators do not include this area in their studies since they have found the pyloric canal to be poorly defined in many patients, and lesions in that area that they thought were gastric actually proved to be duodenal. Our failure to find any cancers in the 35 ulcers in the prepyloric area, however, is contrary to the reports of other investigators, who have found the incidence in this area to be as high as or higher than that on the lesser curvature. The occurrence of cancer in 1 of the 3 ulcers on the greater curvature supports the concept that these lesions are apt to be malignant but are not invariably so. Although there are some variations in the reports of different investigators, we believe the conclusion is justified that there is a lesser incidence of malignant lesions in benign-appearing ulcers located in the region of the pyloric canal and a comparatively high incidence in those on the greater curvature. Otherwise, location is not considered to be of any appreciable diagnostic significance.

Size of Ulcers

Ulcers of 2.5 cm. or more in diameter were classed as large. Of the 162 ulcers 22 (13.6 per cent) were large. Thirteen were treated surgically, 4 refused operation after it was recommended, 4 were not considered to be satisfactory surgical risks, and 1 left before the observations were completed. None of the large ulcers were electively treated medically.

None of the 22 large ulcers proved to be malignant. Sixteen were shown to be benign by operation or autopsy, and 5 healed completely on medical therapy and remained healed. One case could not be followed. Since none of the large ulcers proved to be cancer our findings are in agreement with those of

TABLE 2. *Location of 162 Gastric Ulcers.*

LOCATION	No. OF ULCERS
Lesser curvature	78 (48.1%)
Prepyloric region*	35 (21.6%)
Pyloric canal	33 (20.4%)
Posterior wall	9 (5.6%)
Greater curvature	3 (1.9%)
Anterior wall	2 (1.2%)
Fundus	2 (1.2%)
Total	162

*Considered to be the distal 2.5 cm. of the pyloric part of the stomach and to extend to the pyloric canal.

Branwood,[10] who observed no cancers in a series of 57 large ulcers, and do not support the belief that a high percentage of benign-appearing large gastric ulcers are malignant. In fact, the concept that they are more likely to be benign seems logical, since, if the ulcer caused by a cancer is a large one other signs of cancer are apt to be sufficiently evident to make the diagnosis obvious.

Complications

In 27 (18 per cent) of the 151 admissions the patients were found on x-ray study to have some degree of pyloric obstruction. Fourteen of the 27 patients with pyloric obstruction were successfully treated with medical therapy, and in 10 the ulcer was corrected by surgical resection. In the remaining 3 patients medical therapy failed to remedy a partial obstruction, and operation was either refused or contraindicated.

Sixteen (10.6 per cent) of the admissions were for perforation. Two patients were treated medically (1 had pneumonia, and the other refused operation), and the perforations sealed over and healed. Fourteen were treated surgically. Of the 16 patients with perforation, 5 had an accompanying hemorrhage.

Of the 151 admissions 40 were because of hemorrhage. In 19 (48 per cent) of these the bleeding was classed as severe, in that the red-cell counts were below 3,500,000. There was a mortality of 21 per cent in this group, all 4 deaths occurring in patients who were seriously ill from coexisting chronic disease.

In addition to these complications 32 (23.2 per cent) of the 138 patients had x-ray evidence of active duodenal ulcer while in this hospital. Twenty-nine (21 per cent) others showed duodenal deformity consistent with previous duodenal ulcer. This gave a total of 61 patients (44.2 per cent) who had x-ray findings either diagnostic of active or consistent with pre-existing duodenal ulcer. This high incidence of coexisting or pre-existing duodenal disease accounts in part for the marked variability in the duration and pattern of symptoms in these cases.

Results of Therapy

During the five-year period operation was performed on 43 patients (31.2 per cent) and revealed the existence of a benign ulcer in 35 and of a malignant lesion in 1. In the other 7 cases the surgical procedure was done as an emergency (as for perforation), and it was not possible at operation to determine positively the character of the lesion.

The group that was not treated surgically comprised 108 admissions. In 60 the patients were deliberately treated medically. Among the other 48 admissions surgery was recommended on 13 occasions and was refused; on 20 other occasions surgery was considered to be indicated but the patients were not considered to be satisfactory surgical risks, and on 15 admissions the patients left the hospital before preliminary observations were completed. Some of the patients who were considered to be unsatisfactory surgical risks were not acceptable risks for any type of surgery, whereas in others the contraindication was relative. In all, because of extreme age or coexisting disease, the risk was greater than average.

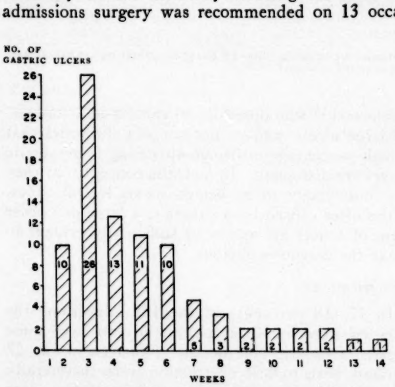

FIGURE 2. *Healing Time of 88 Gastric Ulcers As Determined by X-Ray Examination.*

Altogether, there were 88 ulcers treated medically, by preference or otherwise, and observed radiologically to have healed completely. Of these, 55 per cent healed in four and 88 per cent in six weeks. Among the 67 patients under fifty years of age 61 per cent of the ulcers that healed completely did so within three weeks, whereas among the 71 patients over fifty years of age, only 23.4 per cent healed in this period. There was also a 64 per cent higher incidence of recurrence in the older age group. The healing time of this group of ulcers is shown in Figure 2. It is apparent that in young persons with benign gastric ulcer, healing occurred rapidly — in three weeks in most cases and in six weeks in practically all. We agree with Welch and Allen[4] that the rate of healing is at present perhaps the most useful criterion for determining whether or not an ulcer is benign.

Follow-Up Studies

During the five-year period and the two years after it ended we have made a special effort to follow these patients to determine the ultimate outcome of the disease.

Seventeen of the 138 patients died. Four of these deaths were caused by hemorrhage from the gastric ulcer on the original admission, and in 1, who died eight months after discharge, the family physician stated the cause of death to be "stomach cancer." Although an autopsy was not performed and details concerning the death are not available we have accepted this case as being a carcinoma. In the other 12 cases the cause of death was not related to the gastric lesion. Autopsies were performed in 13 of these 17 cases, giving no evidence of a malignant ulcer in 12 and a carcinoma in situ in 1. In 2 of these autopsied cases the nature of the lesion had previously been proved at operation.

Of the 88 ulcers treated medically and observed to have healed completely, 16 recurred once or more often. In 8 of these the ulcers were shown at operation or autopsy to be benign, and in 2 they proved to be malignant, 1 of these being the carcinoma in situ mentioned above. The 6 remaining patients have refused surgery; in all 6 the recurrent ulcers appeared benign, and 3 healed and remained healed for over a year. Follow-up study on the other 3 patients was considered inadequate.

In addition to the 6 patients who had recurrences and refused operation there were 77 patients whose lesions were not positively identified. Sixty-seven of these, who were followed with x-ray examinations for two or more years (31 for more than three years), gave no evidence of recurrence of the ulcer or any other abnormality of the stomach suggestive of cancer. It is our belief that the absence of x-ray evidence of ulcer or carcinoma two years or more after a gastric ulcer has completely healed is acceptable proof that the lesion was not malignant. There were 13 patients whom we were unable to follow as long as two years, and the information on them is considered insufficient to justify any conclusions.

In the series as a whole 4 of the 138 patients turned out to have cancer. In 3 the diagnosis was proved by surgery or autopsy, and in 1 the evidence is presumptive. Excluding from the study the 13 patients who were followed with x-ray examinations for less than two years and with liberal allowance (50 per cent) for carcinoma in the 6 patients with recurrences who refused operation, the estimated incidence of cancer in this series of cases is about 5 per cent. This includes 42 patients on whom early operation was actually performed or considered desirable because the clinical or radiologic findings were so suggestive of cancer that the possibility was regarded as too strong to justify a trial at medical management.

Of the 60 patients treated medically by choice the ulcers in 2 ultimately were proved or presumed to be malignant, and of the 42 cases in which suspicion was strong enough to constitute an indication for immediate operation the ulcers in 2 were malignant. Although the number of cases of cancer involved is too small for comparison, our studies have convinced us that some of the criteria for differentiating benign from malignant ulcers that were used by us as well as by others are not reliable.

We have not attempted to make detailed comparisons between the benign and malignant lesions, believing that the small number of cancers involved renders such a study statistically unsound. However, the following data relative to the three proved cancers are of interest:

Two of these ulcers were located on the lesser curvature. In a case with ulcer on the greater curvature the carcinoma was found at the time of operation to be metastatic and inoperable. None of the 3 patients had pyloric obstruction. In 2 there was evidence of old inactive duodenal ulcer. Gastric analyses, which were done in 2 cases, showed 39° and no free hydrochloric acid on the fasting specimen. On the patient with no fasting hydrochloric acid there was a 22° response after administration of histamine. Two of the patients had each lost approximately 10 pounds in weight, and 1 had lost 20 pounds. The duration of symptoms was six, six and seven months, respectively, although 1 patient had had symptoms diagnosed by x-ray examination as caused by duodenal ulcer six years previously but had had no symptoms during the intervening period.

Discussion

Few problems of therapy have created such outspoken difference of opinion as that of prompt surgery versus a trial at medical treatment in the management of benign-appearing gastric ulcer. The proponents of immediate operation as assurance against cancer in these cases argue the concept that 10 per cent or more of these ulcers are malignant, that prompt surgery will cure 40 to 50 per cent of the cancers encountered in this type of case, and that the mortality rate of gastric resection does not exceed 2 or 3 per cent.[11] On the other hand proponents of a more conservative attitude believe that prompt, complete and persistent healing of the ulcer is acceptable evidence that it was benign and that, with the exception of selected cases in which the probability of cancer is high enough to justify immediate surgery, a delay for a trial with medical treatment is preferable. They believe that such a delay does not appreciably lessen the chances of a surgical cure — at least the risk is no more than would be offset by the surgical mortality. Actually, there would be a difference of only about 2 per cent in the survival rate of unselected cases treated exclusively by either medical or surgical means (Table 3). The 40 per cent probability of cure of cancer and the 2 per cent surgical mortality represent data from better surgical centers and are undoubtedly more favorable than would hold for the country at large. Or, if the probability of cancer is to be less than 10 per cent, it is evident that any advantage of immediate operation in these cases would be even less than 2 per cent. These data are presented, not to support either method of management but to emphasize the slight difference, in terms of probable survival, between the two methods of treatment and to stress the importance of evaluating each case accurately for the probability of cancer and for operative risk. Only thus can a patient be offered the best chance of survival.

Considering the difficult questions involved and recognizing the inadequacies of our own studies, we are not inclined to make any dogmatic statements concerning the indications for immediate operation

Table 3. *Probability of Survival in 100 Unselected Cases of Benign-Appearing Gastric Ulcer Treated Exclusively by Medical or Surgical Means.**

Type of Treatment	Total Cases	Cases with Cancer	Cancers Cured by Operation	Surgical Deaths	Deaths from Cancer	Total Deaths	Total Survivors
Surgical	100	10	4	2	6	8	92
Medical	100	10	0	0	10	10	90

*Figures based on a 10 per cent probability of cancer, a 40 per cent probability of cure if cancer exists and a 2 per cent surgical mortality.

in these cases. We have, however, come to certain conclusions that will guide us in their management until further data have been accumulated or until better ways are devised for differentiating benign from malignant lesions.

We believe that the decision whether or not to advise prompt operation in cases of benign-appearing gastric ulcer should be made on the basis of an evaluation of all the factors concerned in each case — that is, if the x-ray findings are suggestive of cancer, if there is histamine achlorhydria or if the ulcer is located on the greater curvature. With these exceptions, we believe that patients under fifty years of age should receive a trial at medical management. The most difficult decisions involve patients over fifty years of age in whom age is the only factor suggesting a higher probability of cancer. The decision for or against early operation in this group is probably equivocal, and our choice is usually determined by the estimation of surgical risk. If the patient is a good risk surgery is advised; if he is a poor risk a trial at medical management is preferred.

The duration and pattern of symptoms, the amount of weight loss, the size of the ulcer and the degree of acidity on the fasting specimen are not considered of appreciable significance in differentiating benign from malignant lesions. Prompt, complete and persistent healing is acceptable proof that an ulcer was benign, but patients who are treated medically should be followed at intervals with x-ray examinations for a minimum of two years, and ulcers that fail to heal properly or recur should be treated surgically.

We agree with Boudreau et al.[12] that there is a confusing diversity of opinion among experts concerning the diagnostic significance of various clinical and x-ray findings and that some of the "time-tested" criteria are unreliable. We believe that a continuing re-evaluation of the criteria for determining or suspecting cancer is necessary for the selection of patients with a higher probability of cancer for immediate operation.

It is not considered within the scope of this paper to discuss the pros and cons of morbidity of benign gastric ulcer versus postoperative morbidity as indications for or against surgery. We advise operation if the ulcer is complicated by hemorrhage or unrelieved obstruction or if it fails to heal properly or recurs. We believe that this policy of management minimizes the problem of morbidity.

Summary and Conclusions

A study of 138 patients with gastric ulcers is presented. This represents 151 hospital admissions and includes 162 separate gastric ulcers. Nine patients with ulcerative lesions caused by or associated with obvious cancer and so reported on the initial x-ray examination were excluded from this study.

There were 3 patients with proved and 1 with presumed cancer in the entire group, which included 60 patients treated medically by choice and 42 patients in whom early operation was performed or was considered desirable for assurance against cancer. It is estimated that the incidence of cancer in this series of cases was approximately 5 per cent.

The patient's age and the location of the ulcer are of some diagnostic importance, whereas the duration and pattern of symptoms, the amount of weight loss, the degree of acidity on the fasting specimen and the size of the ulcer are not of appreciable significance in differentiating benign from malignant lesions. Rapid and complete healing, although not infallible, is considered to be acceptable proof that an ulcer was benign.

The decision whether or not to advise immediate operation in these cases should be based on a careful evaluation of all relevant factors in each case. In general it is believed that prompt surgery as assurance against cancer should be advised if the x-ray findings are suggestive of cancer, if there is histamine achlorhydria or if the ulcer is located on the greater curvature. With these exceptions, it is believed that patients under fifty years of age should receive a trial at medical management. In patients over fifty the decision for or against early operation is difficult and is usually made on the basis of whether or not the patient is a good or poor surgical risk. Surgery is also recommended if the ulcer fails to heal under medical therapy or if it recurs.

It is believed that there is need for greater uniformity in the methods of studying these cases and for a continuing re-evaluation of the diagnostic significance of various clinical and x-ray findings.

References

1. Cruveilhier, J. *Anatomie pathologique du corps humain, ou descriptions avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible.* Vol. 1. Paris: Ballière, 1829-1835.
2. Brinton, W. Cancerous infiltration of chronic gastric ulcer. *Tr. Path. Soc. London* 9:200-202, 1858.
3. Morley, J. Surgical pathology of peptic ulcer and gastric carcinoma. *Edinburgh M. J.* 53:273-283, 1946.
4. Welch, C. E., and Allen, A. W. Gastric ulcer: study of Massachusetts General Hospital cases during the ten-year period 1938-1947. *New Eng. J. Med.* 240:277-283, 1949.
5. Ravdin, I. S., and Horn, R. C., Jr. Gastric ulcer and gastric cancer. *Ann. Surg.* 137:904-910, 1953.
6. Ochsner, A., and Blalock, J. Carcinoma of stomach. *J. A. M. A.* 151: 1377-1384, 1953.
7. Lahey, F. H. Diagnosis and treatment of peptic ulcer. *Post-Grad. M. J.* 8:342-352, 1948.
8. Smith, F. H., and Jordan, S. M. Gastric ulcer: study of 600 cases. *Gastroenterology* 11:575-597, 1948.
9. Levin, E., Kirsner, J. B., and Palmer, W. L. Nocturnal gastric secretion in patients with gastric carcinoma: comparison with normal individuals and patients with duodenal ulcer and with gastric ulcer. *Gastroenterology* 12:561-574, 1949.
10. Branwood, A. W. Large gastric ulcer. *Edinburgh M. J.* 57:234-242, 1950.
11. Panel Discussion. Relationship of gastric ulcer to gastric cancer. *Cancer* 3:515-552, 1950.
12. Boudreau, R. P., Harvey, J. P., Jr., and Robbins, S. L. Anatomic studies of benign and malignant gastric ulcerations. *J. A. M. A.* 147:374-377, 1951.

PRIMARY ADENOCARCINOMA OF THE APPENDIX*

Report of a Case with Ruptured Appendix and Peritoneal Carcinomatosis

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PRIMARY adenocarcinoma of the appendix is a rare disease. Young and Wyman[1] carefully searched the literature from 1932 to 1942 and found only 4 bona-fide cases[2-5]; they added a fifth. In 1943 Uihlein and McDonald[6] contributed greatly to the understanding of this disease by classification into three types: carcinoid; malignant mucocele; and adenocarcinoma of the colonic type. Over a thirty-year period at the Mayo Clinic 5 cases of the colonic type had occurred. Ehrlich and Hunter[7] studied 813 gastrointestinal tumors in men of military age during World War II. Of these, 441 were malignant, including 7 primary in the appendix. In 1949 Lesnick and Miller[8] reported 5 cases of adenocarcinoma of the appendix from the Mount Sinai Hospital in New York City. Their cases represented a ten-year period. Other case reports have appeared[9-18] in the American and foreign literature. In 1952 Lawton and Ehrlich[20] reviewed a total of 22 cases and added 3 of their own. Clarke and Simonds[21] found a total of 31 cases as of February, 1953, and added 2. Hilsabeck,[22] at the Mayo Clinic, recently analyzed the cases encountered there between 1910 and 1949. Carcinoids and malignant mucoceles were deleted, leaving 12 cases of the colonic type. Of these 9 were unequivocally primary in the appendix; 3 of the 9 cases were adenomatous polyps that had undergone malignant changes.

The clinical diagnosis of carcinoma of the appendix has not been made preoperatively although other appendiceal disease is often recognized. The true picture is revealed only by pathological study.

That carcinoid may be malignant was re-emphasized in a review of 140 cases by Pearson and Fitzgerald[23] in 1949. They pointed out that surgical removal of an appendiceal carcinoid, unlike that in the small intestine, was curative, and there was no evidence of local or distant metastases. In other parts of the gastrointestinal tract carcinoid may have local spread and distant metastases. The malignant mucocele does not spread to distant parts or to regional lymph nodes.[24] Intraperitoneal spread caused by spillage produces the "jelly-belly" or pseudomyxoma peritonei.

Adenocarcinoma of the appendix may spread to the adjacent cecum or regional lymph nodes, or both. When the cecum is involved it is impossible to be certain which is the primary site of the tumor. Ovarian metastases have been reported.[25] In the case reported below death was due to peritoneal metastases eight months after the appendectomy. We are uncertain of the route of this peritoneal spread because pathological sections revealed tumor cells in the subserous layers and a perforated appendix had existed for sixteen days before removal of the organ. It is a matter of conjecture whether the metastases resulted from bathing of the exposed tumor by peritoneal fluid or from direct extension.

Concerning appendiceal polyps, Woolner[24] states that it is usually impossible to differentiate a polypoid carcinoma from carcinomatous change in an adenomatous polyp. The accepted treatment of adenocarcinoma of the appendix is appendectomy followed by hemicolectomy. If the tumor has invaded the submucosa hemicolectomy should not be omitted. Because of the rarity of this disease and because of the unusual clinical course, we are reporting another case of primary adenocarcinoma of the appendix.

CASE REPORT

M. S., a 65-year-old florist, was admitted to the hospital on April 9, 1950. The past and family history were irrelevant. For 6 weeks before admission the patient complained of dull, constant pain that was neither relieved nor aggravated by eating. There had been no hematemesis, nausea or vomiting. X-ray films of the gastrointestinal tract taken 2 weeks before admission revealed a constant niche in the 1st portion of the duodenum. Two days before admission the abdominal pain became more intense and was accompanied by fever, abdominal distention and vomiting.

Physical examination revealed generalized tenderness and rigidity of the abdominal wall, together with some abdominal distention. A diagnosis of perforated viscus was made, probably a perforated duodenal ulcer. X-ray examination demonstrated absence of free air under the diaphragm. Operation was advised but refused. Treatment consisted of chlortetracycline, streptomycin, penicillin, parenteral infusion of fluids and Wangensteen suction.

There was a gradual lysis of the fever and a disappearance of the signs of peritoneal irritation. After 5 days the patient was able to tolerate small amounts of bland food. He was discharged on his own insistence on the 9th hospital day after 4 days of normal temperature.

A week later he was readmitted to the hospital with a diagnosis of peritonitis. At operation on the following day a pelvic abscess filled with thick, glairy, purulent material was found in the right lower quadrant. The cecum and terminal ileum were indurated, adherent and thickened and covered with an organizing gray exudate. The appendix was perforated, greatly thickened and adherent to the terminal ileum and cecum. The appendix was removed; the abdomen was drained, and antibiotics were again administered. The postoperative course was uneventful, and the patient was discharged in 2 weeks.

The gross specimen consisted of an appendix, measuring 14 cm. in length and 2 cm. in diameter, that was perforated from its middle third to the tip. The serosal surface was dull and reddish purple, and covered partially by yellowish-gray, adherent, fibrinous material. The lumen was moderately broad in the proximal and distal thirds, and contained bloody fluid. In the middle third the lumen was obliterated by a broad-based papilliferous, moderately firm, reddish-gray mass measuring 4.5 cm. in length

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and 1.4 cm. in diameter. The entire circumference of the organ was involved by the tumefaction. The mass appeared to be attached to the mucosa, which was uniformly firm, gray and thickened to 0.8 cm.

Microscopical examination showed the tumor to consist of convoluted bands of tall, columnar cells with eosinophilic cytoplasm. The cells frequently appeared in gland-like or duct-like formation. The stroma was scanty and consisted of thin, fibrovascular strands. The nuclei of the epithelial cells were elongated or oval, vesicular and near the basement membrane in most areas and hyperchromic, enlarged and of irregular shape in others. In still other areas the cells appeared to be heaped up in irregular fashion. In places the tumor appeared to be directly adjacent to submucosa, whereas in other sections a band of mucosa containing orderly mucus-secreting glands, as seen in the normal organ, separated the tumor from the submucosa (Fig. 1). In still other preparations a purulent exudate was noted in the lumen attached to the wall where the mucosa was missing. The submucosa and muscular coats were greatly thickened and contained many plasma cells, lymphocytes, polymorphonuclear leukocytes and eosinophils. Lymphoid follicles were scanty. The subserous tissues were considerably thickened and densely infiltrated with inflammatory cells, as well as foci of well preserved red blood cells. The outer surface consisted of bands of fibrin-enmeshing polymorphonuclear leukocytes. In one preparation several groups of tumor cells with irregular, vesicular and hyperchromatic nuclei were seen in the subserous tissues.

FIGURE 1. *Cross Section of the Appendix, Showing Carcinoma and Normal Mucosa.*

The diagnoses were papillary adenocarcinoma of the appendix, with chronic and acute inflammation, fibrinopurulent periappendicitis and adenocarcinoma in the subserosa.

Ten months later, in February, 1951, the patient was readmitted to the hospital with the signs and symptoms of intestinal obstruction. Exploratory laparotomy was performed 1 week later, and a diffuse peritoneal carcinomatosis was found. A portion of the omentum was taken for study. Eight days later he died. Permission for autopsy was not obtained.

Pathological study of the excised omentum showed adenocarcinoma.

Summary and Conclusions

Another case of primary adenocarcinoma of the appendix is reported. The rarity of this condition is documented by the medical literature. The importance of thorough pathological study of every excised appendix is stressed, since the prognosis and treatment are so dependent on the findings.

References

1. Young, E. L., and Wyman, S. Primary carcinoma of appendix associated with acute appendicitis: report of case. *New Eng. J. Med.* **227**:703-705, 1942.
2. Darnall, W. E., and Kilduffe, R. A. Carcinoma of appendix in girl of twenty. *Am. J. Surg.* **17**:63-65, 1932.
3. Blumenkopf, D. Beitrag zur Kenntnis der primären, echten Carcinome der Appendix. *Ztschr. f. Krebsforsch.* **43**:182-194, 1935.
4. Heine, J. Appendicitis und Karzinom der Appendix. *Zentralbl. f. Chir.* **62**:2601-2603, 1935.
5. Frauenthal, M., and Grausman, R. I. Primary carcinoma in vermiform appendix: report of case. *Am. J. Surg.* **19**:118, 1933.
6. Uihlein, A., and McDonald, J. R. Primary carcinoma of appendix resembling carcinoma of colon. *Surg., Gynec. & Obst.* **76**:711-714, 1943.
7. Ehrlich, J. C., and Hunter, O. B., Jr. Tumors of gastrointestinal tract: survey of 813 in persons of military age during World War II. *Surg., Gynec. & Obst.* **85**:98-106, 1947.
8. Lesnick, G., and Miller, D. Adenocarcinoma of appendix. *Cancer* **2**: 18-24, 1949.
9. Espinosa Fernandez, P.* and Rodriguez H., H. Cáncer del apendice. *Rev. méd. de Chile* **72**:344-347, 1944.
10. Crile, G., Jr., and Glenn, C. G. Primary adenocarcinoma of appendix with development of mucus fistula. *U. S. Nav. M. Bull.* **47**: 328-330, 1947.
11. Chomet, B. Carcinoma of appendix. *Am. J. Clin. Path.* **14**:447-451, 1944.
12. Wells, A. H., and Joffe, H. H. Epithelial neoplasms of appendix. *Minnesota Med.* **30**:176-178, 1947.
13. Maisel, B., and Foot, N. C. Multiple polyposis of colon with malignant change involving colon and appendix: case report. *Ann. Surg.* **126**:262-269, 1947.
14. Lee, G. G., and Blain, J. H. Adenocarcinoma and carcinoid of appendix. *J. Internat. Coll. Surgeons* **13**:197-202, 1950.
15. Marks, E. S., and Whitaker, H. W., Jr. Primary adenocarcinoma of appendix: report of case. *Surgery* **27**:720-725, 1950.
16. McCollum, W., and Pund, E. R. Preinvasive adenocarcinoma of appendix: report of sixteen cases. *Cancer* **4**:261-264, 1951.
17. Sillery, R. J. Primary carcinoma of appendix: report of two cases. *J. A. M. A.* **147**:854-856, 1951.
18. Bosman, G., and Wieberdink, J. Primair carcinoom van de appendix op 26-jarige leeftijd. *Nederl. tijdschr. v. geneesk.* **93**:3980-3983, 1949.
20. Lawton, S. E., and Ehrlich, R. W. Primary adenocarcinoma of appendix. *J. A. M. A.* **150**:189-191, 1952.
21. Clarke, R. G., and Simonds, J. P. Primary adenocarcinoma of appendix: report of two cases. *Am. J. Digest. Dis.* **20**:47-50, 1953.
22. Hilsabeck, J. R. Carcinoma of appendix: analysis of series of cases. *Proc. Staff Meet., Mayo Clin.* **28**:11-16, 1953.
23. Pearson, C. M., and Fitzgerald, P. J. Carcinoid tumors: re-emphasis of their malignant nature: review of 140 cases. *Cancer* **2**:1005-1026, 1949.
24. Woolner, L. B. Carcinoma of appendix: comments on pathology. *Proc. Staff Meet., Mayo Clin.* **28**:17-20, 1953.
25. Waugh, T. R., and Findley, D. Mucocele with peritoneal transplantation in adenocarcinoma of appendix. *Am. J. Surg.* **37**:518-525, 1937.

INTRA-ARTICULAR INJECTION OF CORTISONE IN THE TREATMENT OF RHEUMATOID AND HYPERTROPHIC ARTHRITIS*

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PHILADELPHIA

THE intra-articular use of cortisone in the treatment of rheumatoid and hypertrophic arthritis has not been investigated as widely as the use of hydrocortisone. In 1951 Duff and his co-workers[1] found that intra-articular injection of cortisone reduced the number of white cells in the synovial fluid in cases of rheumatoid arthritis and improved the viscosity and quality of mucin. Similar effects of hydrocortisone were found to be more lasting. The investigators interpreted these findings as support for the belief that both cortisone and hydrocortisone act directly on connective tissue. Early clinical reports[2-4] showed intra-articular injection of cortisone to have transient beneficial effects in rheumatoid arthritis. Later, it was reported to be much less effective than hydrocortisone and devoid of benefit in the treatment of rheumatoid[5-10] and hypertrophic arthritis.[11] In a few cases cortisone caused local irritation[9] and may have increased the inflammation in the joint.[4, 12]

Experience with intra-articular use of hydrocortisone has yielded favorable results in both rheumatoid[5-8, 11-14] and hypertrophic arthritis.[9, 11, 14-16] There is alleviation of pain, swelling, and tenderness, as well as an increase in range of motion. As mentioned above, this compound also reduces the total white-cell count of the joint fluid and lowers the joint temperature in rheumatoid arthritis. One investigator[9] concluded that this method of treatment was of little value in chronic cases of hypertrophic arthritis of the hip joint or knees and that it also failed to relieve 3 patients with acute periarthritis of the shoulder. In another study[13] only 2 of 7 patients with hypertrophic arthritis obtained sufficient improvement to warrant continued injections of hydrocortisone into the knee joints. Transient exacerbation of signs and symptoms in a few cases were the only unfavorable reactions.[15] Caution has been urged for proper selection of cases before intra-articular injection of hydrocortisone is given.[14]

A re-evaluation was undertaken in the Arthritis Clinic of the Philadelphia General Hospital to compare results with those obtained by other investigators. Included in this study are a number of cases of hypertrophic arthritis of the spine. Since there has been a warning against intervertebral injections, reports of intra-articular injection in the spine have been few, but the procedure has been accomplished successfully.[15]

TABLE 1. *Response of Patients with Rheumatoid Arthritis.*

JOINT AFFECTED*	NO. OF PATIENTS	DURATION OF DISEASE	INTERVAL BETWEEN TREATMENTS	PATIENTS IMPROVED	PATIENTS NOT IMPROVED	DURATION OF FREEDOM FROM PAIN
		yr.				
One knee	3	4–9	1 wk.	2	1	1 wk.
Both knees	6†	3–18	1 wk. (4) Biweekly (1)	6		1 wk.
Wrist, right	1	1	1 wk.	1		1 wk.
Multiple joints	1‡	9	1 wk.	1		4 days
Totals	11			10	1	

*One patient had both rheumatoid & hypertrophic arthritis.
†One patient also received cortisone by mouth.
‡Right hip & right knee.

PLAN OF STUDY

Cortisone¶ was injected intra-articularly in 50 patients with rheumatoid and hypertrophic arthritis, most of whom had disease of long duration (Tables 1 and 2). The dosage in all cases was 25 mg., given in aqueous suspension of 1 cc. Injections were given at weekly intervals, but in some cases were given at longer intervals, depending on the duration of beneficial effects. Each case was evaluated at the weekly visit by the same physicians for subjective relief of symptoms, such as diminution of pain and tenderness, and objective signs of improvement, such as decrease in swelling and increase in range of motion. Tables 1 and 2 show the joints involved.

For cases involving the spine a technic of paravertebral injection was developed. In those involving the cervical vertebras, a knowledge of the sensory portion of the cervical and brachial plexuses of nerves is important for the selection of the site

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¶Kindly supplied in aqueous suspension as Cortogen Acetate by the Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

of injection. X-ray examination of the spine is essential. To elicit pain gentle thumping of the spine often suffices and will aid in determining the side and site of injection. One cubic centimeter of cortisone suspension (25 mg.) is employed in a small syringe with a long No. 21 needle. After the skin area has been sterilized 1 per cent procaine hydrochloride may be used as a local anesthetic; however, we prefer to inject the suspension without the aid of local anesthesia, to avoid confusion in the interpretation of results. The needle is inserted into the skin just posterior to the midpoint of the lateral aspect of the neck at the level of the involved vertebra. It is then advanced medially and posteriorly, at an angle of 45°, until the transverse process is encountered, and then directed toward the midline. When resistance is again met the suspension is infiltrated into the area. If blood is withdrawn into the syringe just before the injection, the needle should be withdrawn and the process repeated, to avoid injection of the cortisone into a blood vessel. This method of injection has been considered a paravertebral type of injection. Because of the nature of the spinal articulations true intra-articular injections cannot be accomplished. A similar, but more posterior, approach may be used for the injection of thoracic and lumbar vertebras.

The hip joint has been considered unsuited to this type of treatment because of the difficulty in injecting a suspension directly into the joint space.[14] We have used both an anterior and a lateral approach and, after obtaining satisfactory responses, have continued to employ both methods. When the process involves the sacroiliac joint, the suspension has been injected directly into the articulation.

Joint Response

The value of intra-articular injection of cortisone was analyzed on the basis of response produced in 50 patients. As noted in Tables 1 and 2 a number of patients received injections in more than one joint, a total of 475 injections being given. Favorable response to treatment was considered to be relief of pain and tenderness, an increase in range of joint motion and a diminution of joint swelling. In some cases discomfort was immediately and dramatically relieved. In most, however, pain was alleviated for five to seven days, and a few patients experienced relief for longer periods. After many injections symptoms were exacerbated for periods varying from one to twenty-four hours. In the cases benefited by cortisone injections the combination of the cortisone suspension with an equal volume of 1 per cent procaine hydrochloride was found to be helpful in relieving the transient exacerbation of pain.

Worthy of note is the response of 16 patients with hypertrophic arthritis of the cervical, thoracic or lumbar vertebras. After paravertebral injection improvement was observed in 14. There were no untoward reactions, aside from an occasional transient exacerbation of symptoms immediately after the injection. Satisfactory responses were obtained in 3 patients with disease involving the hip joint; 1 remained improved for eight months after the last injection. Table 1 further illustrates that rheumatoid as well as hypertrophic arthritis is benefited; 1 of these patients received a series of 66 injections at weekly intervals, with no diminution of benefit and no untoward reactions.

Table 2. *Response of Patients with Hypertrophic Arthritis.*

Joints Affected*	No. of Patients	Duration of Disease	Interval between Treatments	Patients Improved	Patients Not Improved	Duration of Freedom from Pain
One knee	6	1¼-4 yr.	1 wk. (3) Biweekly (2)	5	1	1 mo. (1) 2 wk. (1) 1 wk. (1) 3 mo. (1) 10 mo. (1)
Both knees	8	6 wk.-20 yr.	1 wk. 2 wk. (2)	8		3 wk. (1) 1 wk. (5) 4 mo. (1) 2 wk. (1)
Sacroiliac	2	7 yr.	1 wk.	2		3 days (1) 1 mo. (1)
Lumbosacroiliac	1	6 days		1		1 wk.
Cervical vertebras	7	1 mo.-8 yr.	1 wk.	6	1	1 wk. (2) 2 mo. (2) 1 yr. (2)
Lumbar vertebras	6	6 mo.-5 yr.	1 wk.	5	1	1 mo. (1) 2-3 mo. (3) 1 yr. (1)
Hip, right	2	3 yr.	1 wk.	2		1 wk. (1) 8 mo. (1)
Multiple joints†	6	2 mo.-20 yr.	1 wk.	5‡	1‡	3 mo. (1) 1 wk. (3) 1 yr. (1)
Elbow, right	1	35 yr.	1 wk.	1		1 wk.
Totals	39			35	4	

*One patient had both rheumatoid & hypertrophic arthritis.

†Right knee & cervical vertebras (1 case); cervical & lumbar vertebras & sacroiliac joint (1 case); both knees & left shoulder (1 case); sacroiliac joint & lumbar vertebras (1 case).

‡One patient improved in thoracic & unimproved in lumbosacral region.

Discussion

Despite reports to the contrary cortisone injected directly into joints or paravertebrally has been found to bring considerable benefit to patients suffering from rheumatoid or hypertrophic arthritis. Many patients have had not only relief from pain but also an increase in range of joint movement, in some cases sufficient to regain function from a previously useless joint. We have noticed no significant untoward effects in cases of prolonged therapy besides transient local pain after injections.

Hypertrophic arthritis of the spine has a special predilection for the cervical and lumbar regions. When the cervical vertebras are involved pain is experienced in the area of distribution of the cervical or brachial plexus or both. When the process includes the former pain radiates to the occipital, parietal and frontal portions of the scalp. With involvement of the brachial plexus pain radiates down the lateral aspect of the neck into the shoulder and the arm. Except for the use of cumbersome orthopedic appliances little has been done to give relief. It has been gratifying to learn that the pain can be relieved by the injection of cortisone around the area of emergence of the corresponding spinal nerves. It should be emphasized, however, that the success of treatment depends on the recognition of the nerves involved.

Summary

A total of 475 injections of cortisone was made intra-articularly or paravertebrally in 50 patients with rheumatoid or hypertrophic arthritis. Improvement, consisting of relief of pain and tenderness, diminution in joint swelling and increase in range of joint motion, occurred in 45 patients (90 per cent). Paravertebral injection was safe and effective around cervical, thoracic and lumbar articulations. Transient exacerbation of symptoms after cortisone injections may be relieved by the combination of the cortisone suspension with an equal volume of 1 per cent procaine hydrochloride.

References

1. Duff, I. F., Robinson, W. D., and Smith, E. M. Evidence of direct action of adrenocortical steroids on connective tissue: effects of systemic administration of ACTH and cortisone, and of intra-articular cortisone and compound F on joint fluid in rheumatoid arthritis. *J. Lab. & Clin. Med.* **38**:805, 1951.
2. Hollander, J. L., Brown, E. M., Jr., and Stoner, E. K. Cited by Hollander et al.[11]
3. Freyberg, R. H., Patterson, M., Adams, C. H., Durivage, J., and Traeger, C. H. Practical considerations of use of cortisone and ACTH in rheumatoid arthritis. *Ann. Rheumat. Dis.* **10**:1-15, 1951.
4. Ropes, M. W., et al. Discussion of Hollander et al.[5]
5. Hollander, J. L., Brown, E. M., Jr., Jessar, R. A., and Brown, C. Y. Comparative effects of compound F (17-hydroxycorticosterone) and cortisone injected locally into rheumatoid arthritic joint. *Ann. Rheumat. Dis.* **10**:473-476, 1951.
6. *Idem.* Comparative effects of compound F (17-hydroxycorticosterone) and cortisone injected locally into rheumatoid arthritic joint. *J. Clin. Investigation* **30**:650, 1951.
7. Ziff, M., Scull, E., and Bunim, J. J. Effects of intraarticular cortisone and hydrocortisone in rheumatoid arthritis. *Federation Proc.* **11**:405, 1952.
8. Kersley, G. D., and Desmarais, M. H. L. Intra-articular hydrocortisone acetate in rheumatoid arthritis. *Lancet* **2**:269, 1952.
9. Bilka, P. J. Intra-articular use of hydrocortisone in rheumatic disease. *Minnesota Med.* **35**:938-943 and 968, 1952.
10. Forestier, J., Certonciny, A., and Jacqueline, F. Intra-articular injection of cortisone and ACTH in inflammatory rheumatism. *Ann. Rheumat. Dis.* **11**:89, 1952.
11. Hollander, J. L., Brown, E. M., Jr., Jessar, R. A., and Brown, C. Y. Hydrocortisone and cortisone injected into arthritic joints: comparative effects of and use of hydrocortisone as local antiarthritic agent. *J. A. M. A.* **147**:1629-1635, 1951.
12. Stevenson, C. R., Zuckner, J., and Freyberg, R. H. Intra-articular hydrocortisone (compound F) acetate: preliminary report. *Ann. Rheumat. Dis.* **11**:112-118, 1952.
13. Boland, E. W. Rheumatoid arthritis: experiences with hydrocortisone (free alcohol) and hydrocortisone acetate. *California Med.* **77**:1-11, 1952.
14. Ensign, D. C., and Sigler, J. W. Intra-articular hydrocortisone in treatment of arthritis: present status. *J. Michigan M. Soc.* **51**:1189, 1952.

MEDICAL PROGRESS

THE CARDIAC ARRHYTHMIAS*

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LOS ANGELES

SINCE the last Medical Progress report on cardiac arrhythmias appeared in this Journal[1] knowledge concerning these conditions has increased at least as much as during any comparable period in the past. Clinically, new syndromes have been observed, new etiologic factors established, and new therapeutic methods introduced. Interest in the clinical arrhythmias has been intensified by the realization that certain disorders formerly believed irreversible can now be cured. Paralleling and contributing to these clinical advances, significant progress has been made in the field of animal experimentation. The availability of new investigative methods has facilitated experimental study of the mechanisms underlying arrhythmias and their response to drugs.

Many patients undergoing cardiac operations, especially mitral commissurotomy, have spontaneous arrhythmias. It is now feasible to observe the exposed hearts of these patients by direct methods previously applicable only to animals. Knowledge concerning the spontaneous arrhythmias in man is thus being obtained directly, without the necessity of reasoning from the results of animal experimentation. As a fuller understanding of human arrhythmias is gained from observations on patients the mechanism or mechanisms of experimentally produced arrhythmias in animals will become less sig-

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nificant. In this review, therefore, emphasis is placed whenever possible on evidence obtained from studies of the arrhythmias as they occur in man. The mechanism, etiology and clinical aspects of atrial, nodal and ventricular arrhythmias are considered first. Recent observations concerning antiarrhythmic therapy are presented in the final section of the review.

Atrial Arrhythmias

Mechanism

Before 1949 there was almost universal agreement concerning the mechanisms of atrial extrasystoles, flutter and fibrillation. Extrasystoles were believed to arise in an ectopic focus, whence they spread radially in all directions. Flutter and fibrillation were thought to involve a circus movement within the atria as described by Lewis.[2] In recent years a difference of opinion has developed concerning the mechanism of flutter and fibrillation. Although many investigators still accept the circus-movement theory others now maintain that these disturbances result from a repetitively discharging ectopic focus. Recently reported evidence concerning each of these views is discussed under two headings: observations on spontaneous arrhythmias in man and observations on experimentally produced arrhythmias in animals.

Atrial Flutter

The preponderance of observations favoring the circus-movement theory were made before 1949 and therefore are beyond the scope of this report. Nevertheless, since much of the recent literature on atrial flutter concerns the validity of these earlier observations, they are briefly summarized. The existence of a circus movement in cardiac muscle was originally demonstrated under highly artificial conditions by Mines,[3] who actually obtained unidirectional contraction waves in ring preparations cut from the atria of large rays. Lewis subsequently applied this observation to explain the mechanism of experimentally produced atrial flutter in the dog. By timing the intrinsic deflections in direct atrial leads, he traced the course of the flutter impulse through the right atrium and left atrial appendage.[4] The body of the left atrium could not be explored because of technical difficulties. From the available data, Lewis concluded that the excitation wave pursued a circus path. A similar conclusion concerning the course of the flutter wave in patients was drawn from calculations of the momentary atrial electric axis.[5]

In addition to these systematic investigations a number of clinical observations have been cited in support of the circus-movement theory of atrial flutter. For example, the continuous undulations of the baseline in electrocardiograms of patients with atrial flutter are widely believed to constitute evidence of a circus pathway. Antiarrhythmic drugs are commonly assumed to act by lengthening the atrial refractory period or increasing atrial conduction velocity, or both, and thereby terminating circus movements. The usefulness of this concept for teaching purposes may be partially responsible for the widespread acceptance of the circus-movement theory.

Recent observations on spontaneous flutter in man. High-speed cinematographs of the fluttering atria of a patient undergoing mitral commissurotomy have been described in a recent report.[6] As seen in these slow-motion pictures, contraction of the left and right atrial appendages began simultaneously. Both appendages reached maximum systole at the same instant, began to relax synchronously and finally achieved full diastole simultaneously. The authors pointed out that one appendage should contract before the other if a classic circus movement were present. Their slow-motion films, they stated, would reveal any such difference in time of contraction of the two appendages. Hence they concluded that the classic circus-movement theory did not apply in the patient studied. The ectopic-focus theory, on the other hand, was regarded as compatible with the cinematographic findings. Inverted P′ waves appeared in limb Leads 2, 3 and aVF, indicating that the flutter arose in the caudal region. According to the ectopic-focus theory, the contraction wave would travel away from the focus through both atria simultaneously and would terminate in both appendages simultaneously. Synchronous contraction of the two appendages, as seen in the cinematographs, was therefore much more in accord with the theory of ectopic focus than with that of circus movement.

Cabrera Cosio and Sodi Pallares[7] traced the course of the atrial activation wave by means of esophageal and precordial leads in 2 patients with spontaneous atrial flutter. Their findings were believed to demonstrate the presence of circus movement. In a subsequent study of 7 patients, however, Sodi Pallares[8] obtained contrary results. The flutter wave in these cases appeared to arise from a rapidly discharging ectopic focus. A similar conclusion was reached by other workers,[9] who recorded multiple esophageal leads in 10 patients with atrial flutter. The configuration and timing of the complexes indicated that the flutter impulse usually arose from a focus at or near the caudal end of the atrium and traveled to the cephalic end, where it terminated. Less commonly, the impulse was found to originate near the cephalic end and terminate at the caudal extremity. In no case did the tracings suggest that the impulse returned toward the focus, as would occur if circus movement were present. Multiple precordial leads were recorded from 2 of the 10 patients. The configuration of these tracings was likewise considered incompatible with the circus-movement theory.

The validity of one method employed in the preceding studies of spontaneous atrial flutter has been questioned by Hecht.[10] According to this investigator

the intrinsic deflections in precordial and esophageal leads often cannot be timed accurately. Hecht's criticism concerns only the method of timing the flutter wave by means of semidirect leads. His objections were not applied to observations based on the configuration of the flutter complexes.

An analysis of limb and precordial electrocardiograms from 139 patients with spontaneous flutter[9, 11] revealed isoelectric intervals in 95 per cent. The length of the isoelectric period usually varied inversely with atrial rate. As interpreted by the investigators these isoelectric intervals corresponded to atrial diastole. Diastolic periods, it was pointed out, are compatible with the ectopic-focus theory of flutter but would not occur if a continuous circus movement were present. Consideration was given to the possibility that atrial activity actually exists during the isoelectric interval without affecting the electrodes. This explanation was regarded as highly improbable since precordial and limb leads are supposed to register activity throughout the atria. In 5 per cent of the 139 cases analyzed, continuous undulations without isoelectric intervals were observed in all leads. Most of these tracings were recorded from patients with extremely rapid atrial rates or after administration of quinidine. Many electrocardiograms presented isoelectric periods in some leads and continuous undulations in other leads, indicating that both patterns represented the same disturbance of rhythm. The conclusion was therefore drawn that the arrhythmia arises from a rapidly discharging ectopic focus regardless of whether or not pure flutter undulations are present in the electrocardiogram.

Evidence has been advanced that the undulatory pattern of flutter consists of two components, a P′ wave of depolarization followed by a Ta wave of repolarization.[9, 11] Failure to recognize this distinction was thought to invalidate Lewis's calculations of the momentary atrial electric axis of the flutter wave. The P′ and Ta components were delineated in tracings from Lewis's patient and the electric axis recalculated, only the P′ wave of depolarization being used. The results appeared compatible with the theory of a repetitively discharging ectopic focus but not with the circus-movement theory.

Another observation cited as evidence against the circus-movement theory concerns the length of the P′-P′ interval in electrocardiograms of patients with clinical atrial flutter.[9, 11] If the flutter wave pursued a circus pathway at a constant velocity, the authors reasoned, the time required for a complete circuit would be approximately twice that required for the caudocephalic half of the journey. They tested this hypothesis by timing the intrinsic deflections in esophageal leads from 7 patients with flutter. The impulse was found to traverse the caudocephalic length of the atrium in approximately 0.04 to 0.06 second. Thus, the entire circuit, as measured by the P′-P′ interval, should have required only 0.08 to 0.12 second; P′-P′ intervals of 0.08-0.12 second would occur if the atrial rate was between 500 and 750 beats per minute. Actually, the rates in the patients studied varied from 200 to 300. The authors recognized that inaccuracies in timing the intrinsic deflections may have affected their calculations. Such errors, however, were not considered sufficiently serious to account for the marked discrepancy between hypothetical and actual flutter rates. They concluded that no circus movement occurred, or that the last half of the circuit was much slower than the first.

Several cases of clinical flutter that presented P′ waves similar or identical in configuration with normal P waves were reported. It was pointed out that the configuration of the P or P′ wave is determined by the course of atrial excitation. Since the P wave of normal sinus rhythm does not represent a circus movement, the flutter P′ wave in these cases was also thought not to represent circus movement.

Recent studies[11] of the pharmacology of quinidine and procaine amide suggest that the antiarrhythmic action of these drugs may not be related to their effect on the refractory period or atrial conductivity. A close correlation was found between the excitability-depressing effect of the drugs and their ability to terminate flutter and fibrillation. This has been considered evidence that antiarrhythmic agents act by depressing excitability of an ectopic focus, thereby slowing the rate of discharge so that the sinus node can resume its pacemaking function.

Recent observations on experimental flutter in animals. The examples of experimental atrial flutter observed in Lewis's laboratory were initiated by electric stimulation and studied during their brief poststimulatory phase. In recent years this classic technic has been supplemented by two methods of producing flutter: local application of aconitine to the atrium, as employed by Scherf and his associates,[12] and the procedure of Rosenblueth and Garcia Ramos,[13-15] which consists of crushing or blocking the intercaval bridge before electric stimuli are applied. Since the mechanism of experimental arrhythmias may depend on the method of production the use of three different technics by different investigators has yielded a number of conflicting observations.

Among the first of the workers who seriously challenged Lewis's circus-movement theory was Scherf, who caused atrial flutter in dogs by establishing an ectopic focus with aconitine.[16-20] When the aconitine focus was isolated or cooled the flutter disappeared. Reappearance of the arrhythmia after the cooling stopped was also noted.[16] It was further demonstrated that stretching of the musculature in the region of the ectopic focus increased the flutter rate or caused conversion to fibrillation.[17] These observations on aconitine-produced flutter

have been regarded as evidence against the presence of a self-perpetuating circus movement.

Wilson[21] proposed a modification of the original circus-movement theory that appears compatible with Scherf's findings. He suggested that each flutter beat may arise from the ectopic focus, pursue a circus pathway around the atrium and terminate on completion of the circuit. According to this hypothesis flutter presents both a repetitively discharging ectopic focus and a circus movement. Another version of the circus-movement theory was offered by Katz and Pick,[22] who suggested that multiple simultaneous circulating waves may be present in flutter. The multiple re-entries were supposed to perpetuate the vulnerable period of the cardiac cycle. Either the sinus node or an ectopic focus presumably could give rise to the initiating impulse.

Evidence incompatible with the modified versions of Wilson and Katz, as well as with Lewis's classic circus-movement theory, has been reported by other investigators.[9, 11] These workers studied many experiments in which flutter was produced in dogs alternately by Lewis's technic of electric stimulation and by Scherf's aconitine method. Direct leads were recorded throughout the interatrial septum and both atria, including the body of the left atrium, which had not been explored by Lewis. Conclusions were based on the timing of the intrinsic deflections and the configuration of the complexes. Both factors indicated that the flutter wave originated at the ectopic focus and spread out radially in all available directions simultaneously. Another direct method used to observe the flutter wave was high-speed cinematography, a technic permitting visualization of atrial activity at a small fraction of its actual rate. The flutter contraction wave seen in the cinematographs, like the excitation wave traced with direct leads, appeared to travel away from the focus in all available directions simultaneously. Evidence of a primary wave that returned toward the focus or of smaller circulating waves was not found in either the direct leads or the cinematographs. Dawes[23] has argued that cinematographic studies do not rule out the presence of a circus movement if the mass of muscle involved is too small to be seen.

The experimental observations of Rosenblueth and Garcia Ramos provide more powerful support for the circus-movement theory than any evidence reported since the work of Lewis. These investigators found that prolonged episodes of poststimulatory flutter occurred when the intercaval bridge was crushed or blocked with cocaine before electric stimulation. The arrhythmia produced by this method was much longer in duration, and therefore much more readily observed, than that obtained by Lewis. Other workers[24, 25] have recently confirmed the finding that preliminary crushing or blocking of the intercaval bridge facilitates the production of poststimulatory flutter. Scherf,[26] however, found the method only moderately effective. Using their original technic to produce flutter, Rosenblueth and Garcia Ramos[14, 15] timed the excitation wave by recording multiple direct leads around the crushed or blocked region. Their results indicated the presence of circular movements. The intercaval crush or block was believed to provide an obstacle to short-cuts across the atrium, thereby preventing deviations from the circus pathway that might terminate the arrhythmia. An alternative explanation, which does not assume the existence of a circus pathway, was proposed by Scherf[26]: that the crushed or blocked region may be capable of rapid impulse formation, thus acting as a repetitively discharging ectopic focus. Scherf's hypothesis may account for the proarrhythmic effect of intercaval damage before electric stimulation. It nevertheless fails to explain the timing of the intrinsic deflections in direct atrial leads that Rosenblueth and Garcia Ramos advanced as evidence of a circus movement.

Atrial Fibrillation

The circus-movement theory of atrial fibrillation appears to have originated largely because of the close relation between flutter and fibrillation in both man and laboratory animals. Believing that flutter involved a circus movement Lewis[27] suggested that fibrillation must present a similar mechanism. He thought that the circus rhythm in flutter was regular whereas that of fibrillation was irregular. Clinical evidence supporting this hypothesis was obtained by Lewis, Drury and Iliescu[27a] from a study of the F waves in the fibrillation electrocardiogram. Few additional observations on the mechanism of atrial fibrillation were reported until a few years ago.

Recent observations on spontaneous fibrillation in man. Direct observations on the fibrillating atria of 5 patients undergoing cardiac operations have been reported in the literature.[28] Both high-speed cinematographs and direct-lead electrocardiograms were recorded. As described by the observers the cinematographs showed more or less organized contraction waves occurring at an irregular rate of 350 to 400 beats per minute. Each contraction appeared to differ somewhat from the preceding wave in course, vigor and rate of propagation. Cinematographs from 1 patient exhibited a second type of mechanical activity occurring simultaneously with the contraction waves; this consisted of rapid, heterorhythmic contractions and dilatations of minute muscle segments, most clearly seen along the cephalic border of the left atrial appendage. The direct atrial leads contained slightly irregular complexes varying from 0.2 to 0.4 mv. in amplitude and occurring at a frequency of 350 to 400 per minute. These deflections were presumed to correspond to the F waves seen in standard leads of fibrillation and also to the contraction waves observed in the

cinematographs. In addition to F waves the tracings presented smaller deflections of highly variable contour occurring at rapid and irregular rates. No evidence of a circus movement was seen in either the cinematographs or the direct leads. Before these studies Groedel and Miller[29] recorded direct atrial leads from a patient with spontaneous flutter fibrillation. Complexes of various sizes and shapes were registered in tracings from different sites in the left atrium. The variability of the complexes was considered incompatible with the circus-movement theory but was believed to indicate a multifocal disturbance.

A cathode-ray oscilloscope was used to record two esophageal leads in each of 24 patients with spontaneous fibrillation. The oscilloscope, being entirely free from inertia, proved most satisfactory for demonstrating the extremely rapid activity of the fibrillating atria. Esophageal-lead oscillograms from the 24 patients were found to display virtually the same phenomena as the previously described direct-lead electrocardiograms. Little or no constant sequence of electric activity in different parts of the atrium was observed.

Recent observations on experimental atrial fibrillation in animals. Atrial fibrillation, like flutter, has been produced experimentally in dogs by the alternative methods of aconitine and electric stimulation.[11] The motion observed in high-speed cinematographs of the fibrillating atrium was described as chaotic, bizarre and heterorhythmic. This activity was markedly different from the orderly sequence of events demonstrated during all other experimental atrial rhythms. Two extreme types of fibrillary activity were distinguished: asynchronous contractions and dilatations of minute muscle segments, best seen under high magnification; and broad contraction and relaxation waves involving large portions of the musculature. These extreme forms, as well as all intermediate types of activity, were continuously visible throughout the atria. If a circus movement had been present, the observers emphasized, the head and tail of the wave, the isoelectric gap and the daughter waves should have revealed themselves in the cinematographs. None of these features, however, were found.

The electric activity recorded in the fibrillating atria was likewise considered incompatible with a circus movement. Direct leads registered on both electrocardiographic and oscillographic apparatus exhibited continuous deflections of low but varying potential and extremely high but irregular frequency. These minute deflections were superimposed on relatively large complexes of variable configuration occurring at slower rates. Waves of intermediate amplitude and frequency were also described. The large, minute and intermediate deflections in the direct leads were assumed to correspond to the extreme and intermediate types of mechanical activity seen in cinematographs of the fibrillating atrium. It was further suggested that the large complexes in the direct leads might be a counterpart of the F waves in the limb and precordial leads.

Results conflicting with those of the preceding electrocardiographic and oscilloscopic studies were reported by Rosenblueth and Garcia Ramos.[13-15] These workers produced atrial fibrillation by electric stimulation after the intercaval bridge had been crushed or blocked. From an examination of direct leads recorded during the experiments, they concluded that their method yielded a circus movement.

An explanation of the chaotic activity in the fibrillating atria has been derived from experimental observations of the transition between flutter and fibrillation.[11] Direct leads and high-speed cinematographs were recorded as electric stimuli were applied to the atrium at progressively increasing rates. As the rate of stimulation gradually approached the fibrillation threshold (defined as the rate immediately before the onset of fibrillation and found to approximate 600 per minute) the interval between stimulus and intrinsic deflection in the direct leads progressively lengthened. The P' waves became increasingly widened and splintered. A mechanical counterpart of these changes was observed in the cinematographs. The rate of propagation of the contraction waves gradually became slower and the period of atrial diastole grew shorter. At the fibrillation threshold the stimulus-intrinsic interval could no longer be measured, and the organized contraction waves suddenly gave way to chaotic activity. The progressive electrocardiographic and cinematographic changes observed before the onset of fibrillation were believed to indicate a progressively increasing degree of conduction failure. When the fibrillation threshold was reached conduction failure presumably had become so pronounced that the atrial myocardium could no longer conduct impulses in a co-ordinated manner. Hence the disorganized electric and mechanical phenomena of fibrillation ensued. Additional evidence for this hypothesis was obtained by study of the effects of various drugs on the fibrillation threshold and on conduction recovery. Strophanthin, digitalis and quinidine were found to lower the fibrillation threshold while depressing conduction recovery. Acetylcholine, on the other hand, greatly raised the fibrillation threshold and enhanced conduction recovery. From these experiments the conclusion was drawn that failure of conduction must take place before fibrillation can occur. The rarity of fibrillation in children as compared with aged patients was considered a probable function of the higher degree of myocardial conductivity in younger persons.

Electrocardiograms of 5 patients recorded during transitions from flutter to fibrillation have been described.[11] The atrial rates immediately before the onset of fibrillation, considered to approximate the fibrillation threshold, ranged from 360 to 432 beats

per minute. All 5 patients had heart disease, and some were receiving digitalis; these factors were believed to have influenced the fibrillation threshold. In other patients a fibrillation threshold could not be demonstrated, for the arrhythmia started abruptly after a single extrasystole falling during the "vulnerable" time period. The extrasystole was thought to induce a degree of conduction failure sufficient to precipitate fibrillation.

Atrial Extrasystoles and Tachycardia

Little or no controversy exists regarding the mechanism of extrasystoles. These beats are generally believed to arise from an ectopic focus and to spread in all directions. Lewis[30] suggested that atrial tachycardia may be considered as a series of extrasystoles occurring at a relatively rapid rate. He called attention to clinical electrocardiograms showing transitions from extrasystoles to tachycardia in which the complexes of both arrhythmias presented the same configuration.

Barker, Wilson and Johnston[31] supported the alternative hypothesis that certain cases of atrial tachycardia may be due to circus movement in and out of the sinoatrial or atrioventricular node. They cited the following clinical characteristics as evidence of a circus movement: the abrupt onset and termination of attacks; the remarkable stability of rate; the slowing of atrial rate and termination of paroxysms by quinidine; and the occasional alternation of cycle length. The circus pathway was assumed to involve one of the specialized nodes because of the slowing of atrial rate and termination of attacks by vagal stimulation and digitalis, the acceleration of the rate by exercise, the relatively slow rate and long cycle length, and the separation of the atrial deflections by isoelectric intervals.

Other workers contended that the preceding clinical characteristics of tachycardia are at least equally compatible with the ectopic-focus theory. They further reported that esophageal leads in patients with spontaneous tachycardia show the impulse to arise at one end of the atrium and terminate at the opposite end.[11] In no case did the configuration of the tracings indicate that the impulse returned toward its site of origin as it would if circus movement had been present. The ectopic focus of the tachycardia was usually found at the cephalic extremity of the atrium but was occasionally in the caudal region.

Atrial extrasystoles and tachycardia have been produced experimentally in human subjects by mechanical stimulation of the atria during thoracic surgery.[11] Esophageal and limb leads were recorded during the arrhythmias. The esophageal leads resembled those from patients with spontaneous extrasystoles and tachycardia, indicating that the impulse traversed the atrium from the focus to the opposite extremity and did not return to its site of origin. Leads 1, 2 and aVF showed upright P′ waves when the focus was produced at the cephalic end of the atrium. Inverted P′ waves occurred in these leads when the focus was at the caudal end. Arrhythmias arising from foci in the middle of the atrium often failed to yield visible P′ waves in limb leads.

High-speed cinematographs and direct leads of experimentally produced atrial extrasystoles and tachycardia in dogs have been described.[11] As in flutter the contraction and excitation waves of both arrhythmias arose at the focus and spread radially outward in all available directions simultaneously. No evidence of a circus movement was noted.

Relation between the Arrhythmias

That a close relation exists between the various atrial arrhythmias has long been suspected. At the turn of the century, Trendelenburg[32] and Rothberger and Winterberg,[33] of the Viennese school, suggested that all the atrial arrhythmias might result from a discharging ectopic focus. Which arrhythmia would prevail was believed to be chiefly a function of the rate of discharge of the focus. If the focus discharged at a rate slower than the sinus node, extrasystoles were supposed to occur. At progressively faster rates, tachycardia, flutter and fibrillation would presumably be observed. This theory was based on the experimental observation that all four arrhythmias could be elicited by electric stimulation of the atrium at different rates. In 1912 Lewis[34] stated, "The conclusions that (all the auricular arrhythmias) arise essentially in the same manner... are clearly suggested by the facts at our disposal." When he later attributed to flutter and fibrillation a mechanism different from that of extrasystoles and tachycardia, and when attention was called to certain clinical differences, the theory of the unitary nature of the arrhythmias was largely abandoned.

Recent clinical and experimental studies have again raised the question of the relation between the arrhythmias. A number of observations suggest the unitary nature of all four disorders. Other observations have been considered to indicate the operation of two or more mechanisms in different arrhythmias or in different examples of the same arrhythmia. The evidence pertinent to these opposing theories is briefly reviewed.

Observations in man. A close relation between the clinical forms of extrasystole and tachycardia has been assumed because of the frequent occurrence of both arrhythmias in the same patient and sometimes in the same tracing. Similarly, transitions between flutter and fibrillation often occur clinically and are occasionally recorded in the electrocardiogram. Atrial tachycardia and flutter, on the other hand, rarely appear in the same patient. The relation between these two arrhythmias has recently been discussed at length.[11]

It has been stated that clinical tachycardia and flutter were reported to differ only in rate of dis-

charge from an ectopic focus, the former occurring at slower rates than the latter. This statement is erroneous. The authors in question[11] actually pointed out that some paroxysms of tachycardia may present more rapid rates than flutter. Patients with tachycardia at rates of 300 per minute and others with flutter at rates as low as 200 per minute were described. Moreover, attention was called to a number of clinically important dissimilarities between the two arrhythmias. Tachycardia appears most commonly in young persons with otherwise normal hearts. Flutter, in contrast, is usually found in elderly patients with organic heart disease. Tachycardia arises most often from a focus in the cephalic region of the atrium; flutter usually originates in the caudal region. Increasing vagal tone, as by carotid-sinus stimulation, either abolishes tachycardia or has no effect on the cardiac rhythm. When the same measure is administered during flutter it seldom restores sinus rhythm and may precipitate fibrillation.

Despite these clinical differences a marked similarity was noted in the manner of atrial activation during clinical tachycardia and flutter. Esophageal leads from numerous patients indicated that both arrhythmias arose from a repetitively discharging ectopic focus, usually at one extremity of the atria. The excitation waves of both arrhythmias appeared to travel away from the focus to the opposite extremity. No evidence of a circus movement was found in either arrhythmia. Thus, the events in the atria during clinical tachycardia and flutter were considered similar.

As hypothesized by the observers, the fundamental clinical difference between these two arrhythmias concerns the stability of atrioventricular conduction during atrial tachycardia as compared with flutter. A firm binding of unknown nature was believed to exist between the atria and ventricles in typical cases of clinical tachycardia. In atrial flutter the binding was assumed to be broken or "loose." This hypothesis was based on the observation that physiologic atrioventricular block rarely occurs in typical clinical tachycardias, even when the atrial rate is extremely rapid. In clinical flutter, however, block usually is present even at relatively slow rates. Furthermore, carotid-sinus stimulation does not affect atrioventricular conduction in patients during paroxysms of atrial tachycardia, but may cause prolongation of the PR interval in the same patient after termination of the bout.

The preceding hypothesis concerns only the common type of paroxysmal tachycardia familiar to all clinicians. Tachycardias of this type do not present atrioventricular block. Several exceptional types of tachycardia, with partial or complete block, have been reported. The cases in Lown's[35] series were atypical in several respects. Most of the arrhythmias apparently resulted from digitalis intoxication and electrolyte imbalance. The patients showed a high incidence of heart disease as well as other characteristics different from those of the usual case of clinical tachycardia. Another atypical case of tachycardia was cited[36] in which 2:1 atrioventricular block developed in response to Neo-Synephrine, a drug that indirectly increases vagal tone. The tracing of tachycardia with 2:1 block was indistinguishable from that of flutter. Several examples of tachycardia with pathologic block due to posterior myocardial infarction were observed.[11] In these cases the infarct not only destroyed the structural continuity of the atrioventricular conduction system but also gave rise to the ectopic focus. Organic lesions of the conduction system were also found in 6 cases of tachycardia with complete heart block. All 6 patients yielded tracings indistinguishable from flutter with atrioventricular block. The electrocardiographic resemblance between tachycardia with block and flutter was regarded as evidence that the fundamental difference between these arrhythmias concerns atrioventricular conduction rather than atrial activation.

In contrast to the common clinical type of tachycardia, flutter is generally associated with physiologic atrioventricular block. The instability of atrioventricular conduction is further demonstrated by the common occurrence of variations in ventricular response. Carotid-sinus stimulation usually increases the degree of block. Treatment of flutter with quinidine may cause a progressive decrease in the degree of block — for example, from 4:1 to 2:1 and finally to 1:1. The disappearance of block leaves the patient in a serious condition, with an extremely rapid ventricular rate. At this stage the electrocardiogram may be indistinguishable from that of tachycardia. A 1:1 ventricular response during flutter is transient; block promptly reappears and varies — for example, from 1:1 to 2:1 to 4:1 and back again to 2:1. Such variations are common during flutter but never occur during tachycardia.

Several other observations suggest that the atrial disturbances during clinical tachycardia and flutter may not differ in mechanism from one another or from extrasystoles and fibrillation. Permanent fibrillation occurred in some patients after a transition from extrasystoles through tachycardia, flutter and paroxysmal fibrillation. Quinidine and less frequently digitalis may terminate any of the arrhythmias. Cases were observed[37] in which quinidine converted fibrillation to normal sinus rhythm, with a gradual transition through flutter, tachycardia and extrasystoles. Finally, the fact that all four arrhythmias have been produced in different patients by accidental stimulation of the atrium during cardiac catheterization or surgical procedures has been considered evidence of a similarity in mechanism of the atrial disturbance.

Observations in laboratory animals. The theory that all atrial arrhythmias result from a repetitively

discharging ectopic focus has been considered to apply to experimental arrhythmias produced under certain conditions. Flutter and fibrillation initiated by the method of Rosenblueth and Garcia Ramos[13-15] were reported to present a self-perpetuating circus movement, which is incompatible with the ectopic-focus theory. On the other hand, flutter and fibrillation produced by Lewis's classic method of electric stimulation or by aconitine were found to differ from extrasystoles and tachycardia only in rate of discharge from an ectopic focus.[11] The evidence presented to support this conclusion consisted, first, of the fact that all four disorders could be elicited by electric or chemical stimulation of a single ectopic focus and, secondly, similarities in the mechanical and electric activity of the atria during atrial extrasystoles, tachycardia and flutter.

Scherf's observations on aconitine-produced arrhythmias were consistent with the ectopic-focus theory but indicated that the nature of the focus may vary in different arrhythmias. This investigator reported that atrial tachycardia is the result of rapid, interrupted discharge of an ectopic focus. He suggested that flutter, in contrast, is due to continuous discharge of an ectopic focus.[16, 26] He further considered that fibrillation produced with aconitine is unifocal in origin whereas the same arrhythmia produced with acetylcholine is of multifocal origin.[20] Another study by Scherf et al.[38] revealed no correlation between the rate of an ectopic rhythm and its response to acetylcholine or vagal stimulation.

Conclusions. If a symposium on the mechanism of opinion. Extrasystoles and probably tachycardia would have been attributed to a repetitively discharging ectopic focus flutter and fibrillation were generally thought to involve a self-perpetuating circus movement. The experimental and clinical observations reported since 1949 have effected a striking modification of these opinions. In contrast to the general agreement prevailing five years ago, a symposium reported during 1953 reflected widely varying views concerning the mechanism of atrial arrhythmias.[39] Four papers were included in the symposium. Only one author stated unequivocally that flutter and fibrillation in both man and laboratory animals involved a circus movement.[40] Another writer[41] attributed all four atrial arrhythmias in man to a repetitively discharging ectopic focus. The mechanism of flutter and fibrillation in animals, however, was thought to vary with the method of production. A third author[10] agreed that experimental flutter and fibrillation may exhibit different mechanisms when produced by different methods. Reasoning from this conclusion, he suggested that clinical arrhythmias also might differ in mechanism in different patients. The authors of the fourth paper[42] considered no single theory adequate to account for all the experimental and clinical evidence concerning flutter and fibrillation. A compromise hypothesis was therefore proposed. Both arrhythmias were assumed to initiate ffrom a discharging ectopic focus and to persist through a mechanism of multiple re-entries.

We have attempted to present impartially the conflicting evidence concerning the mechanism of atrial flutter and fibrillation. After critically appraising this evidence, it is our opinion that the following conclusions may be drawn:

Spontaneous flutter in man results from a rapidly discharging ectopic focus. No circus movement is present. This conclusion is based on the electric activity and motion of the fluttering atria as actually observed in patients. A returning wave, which is essential to circus movements, cannot be demonstrated in esophageal leads; the tracings show that flutter waves arise from an ectopic focus at one end of the atria and terminate at the opposite end. In a patient with flutter observed during surgery, both atrial appendages contracted simultaneously; if the classic circus movement had been present one atrial appendage would have contracted before the other. An isoelectric period, interpreted as atrial diastole, is seen in most clinical electrocardiograms; diastolic periods presumably would not occur in the presence of a self-perpetuating circus movement. Finally, the continuous undulations occasionally seen in tracings of flutter do not represent a continuous circulating wave, as supposed by proponents of the circus movement theory, but are composed of rapidly recurring P′ waves of depolarization followed by Ta waves of repolarization.

Spontaneous atrial fibrillation in man is a chaotic, heterorhythmic disturbance consisting of two general types of activity: large waves occurring at irregular rates of about 300 per minute, and small waves appearing at greater frequencies. These two types of waves have been seen in direct-lead electrocardiograms and high-speed films recorded during surgery as well as in esophageal-lead oscillograms. No electric or mechanical evidence of a circus movement is present. Clinical fibrillation appears to represent an advanced degree of conduction failure occurring when the atrial rate reaches a certain critical level, termed the "fibrillation threshold." In patients showing transitions from flutter to fibrillation, the "fibrillation threshold" is the approximate rate at which flutter ceases and fibrillation begins.

The mechanism of experimentally produced atrial flutter and fibrillation in animals may vary with the method of production.

Etiology

Atrial arrhythmias have frequently been observed during cardiac catheterization.[42a, 43] These disturbances are often attributable to the location of the

catheter tip in the atrium. In some cases, however, the arrhythmia occurs while the catheter tip is still in the vena cava, suggesting a reflex origin. Normal rhythm usually reappears when the catheter is no longer in a position to cause irritation. The atrial disorders, apparently, are of relatively little clinical importance, being less common and less serious than ventricular arrhythmias that arise during cardiac catheterization.

Emotional disturbances as an etiologic factor in atrial arrhythmias have been studied by Stevenson et al.,[44] Duncan and Stevenson[45] and Altschule.[46] These investigators concluded that emotional stress often contributed to the production of supraventricular arrhythmias in patients with organic heart disease and, less frequently, in patients with normal hearts. Pregnancy was also found to predispose to paroxysmal tachycardias.[47]

Digitalis may produce a wide variety of atrial arrhythmias. Lown and his associates[35] described an especially interesting arrhythmia consisting of atrial tachycardia with atrioventricular block apparently resulting from digitalis administration in patients with lowered serum potassium levels. The cases in this series differed from typical ectopic tachycardia in the following respects: most of the patients had advanced congestive heart failure, digitalis intoxicaton and electrolyte imbalance, and were frequently benefited by potassium therapy. Flutter as a manifestation of digitalis toxicity has been considered uncommon enough to warrant a case report.[48] This arrhythmia has also been observed after indirect cardiac trauma.[49]

The importance of masked hyperthyroidism as an etiologic factor in atrial fibrillation has been reemphasized by Bortin et al.[50] By means of determinations of radioactive iodine uptake and protein-bound iodine, these investigators demonstrated the presence of previously undetected hyperthyroidism in 8 of 55 patients with fibrillation. Kissane, Brooks and Clark[51] reported a normal incidence of hyperthyroidism among 361 patients with supraventricular tachycardia. Nevertheless, in our experience, masked hyperthyroidism should also be sought in cases of paroxysmal atrial tachycardia of unexplained origin.

Two cases of fibrillation associated with hemochromatosis were reported by Griffin, Nelson and Seal[52] and Levin and Golum.[53] In each the hemosiderin pigment was demonstrated at autopsy in the atrial and ventricular myocardium. No other etiologic factor for the arrhythmia could be discovered.

Arrhythmias associated with the Wolff–Parkinson–White syndrome have lately received considerable attention. Assuming that the syndrome results from conduction through an aberrant anatomic atrioventricular connection, Fox and his associates[54] suggested that associated arrhythmias may be due to a decrease in "vagus substance." The deficiency of vagus substance is supposed to cause a block in the aberrant conduction system, permitting its supraventricular portion to act as an ectopic focus. Supraventricular arrhythmias may thus be set up, and the impulses transmitted to the ventricles over the normal atrioventricular conduction system. The authors further hypothesized that both the aberrant and the normal conduction systems may become blocked. In this event a ventricular ectopic focus may give rise to ventricular arrhythmias. Other investigations[55] have yielded evidence that a disturbance in the atrioventricular node may be responsible for the Wolff–Parkinson–White syndrome. Supraventricular arrhythmias associated with the syndrome were found to occur when the atrioventricular node functioned as the cardiac pacemaker.

Clinical Aspects

A new electrocardiographic lead devised by Lian et al.[56] has been reported useful in the diagnosis of some arrhythmias that fail to show distinct P′ waves in conventional leads. The right-arm electrode is placed over the manubrium, and the left-arm electrode in the fifth intercostal space in the parasternal line. Tracings are taken as Lead 1 and are designated Lead S_5. Presumably because of the proximity of the electrodes to the atria Lead S_5 magnifies the atrial deflections. This lead may prove helpful when P waves cannot be clearly demonstrated in unipolar subclavicular and high posterior chest leads with the indifferent electrode at Wilson's central terminal.

The problem of paroxysmal supraventricular tachycardia in infancy and childhood has been reviewed by Nadas and his co-workers.[57] These authors noted that the arrhythmia usually occurs during the first four months of life and may be asymptomatic. No associated disturbance was found in 50 per cent of cases. The usual clinical picture was characterized by cyanosis, vomiting, tachypnea, fever and leukocytosis. Recurrence after the first year was observed chiefly in children with the Wolff–Parkinson–White syndrome or congenital heart disease. These authors as well as Silverman and Werner[58] pointed out that arrhythmias in young children often remain undiagnosed because they are not commonly suspected, owing to the difficulty of clinical diagnosis and to the fact that routine electrocardiograms are seldom made. One notable infant described by Silverman and Race[59] presented supraventricular tachycardia with a ventricular rate of 365, apparently the most rapid ever reported. Hay and Keidan[60] described 3 cases of ectopic atrial tachycardia in children with rates of 150 to 200 persisting for years without evidence of congestive heart failure. In another case,[61] in which the heart of a child dying of atrial tachycardia was examined post mortem, an old extravasation of blood, probably representing the ectopic focus, was found in the atrial myocardium. Leach and Gibson,[62] discussing a case of par-

oxysmal atrial flutter with variable atrioventricular block, called attention to the fact that all supraventricular arrhythmias in infants are not tachycardia.

Askey[63, 64] has analyzed the incidence of atrial arrhythmias among 1247 patients with myocardial infarction. Flutter and tachycardia were relatively uncommon, occurring in 20 cases and 5 cases respectively. Fibrillation was present in 84 cases. Both flutter and tachycardia carried a high mortality rate, which was in direct proportion to the rapidity of the ventricular rate. In the fatal cases death usually occurred soon after onset of the arrhythmia. The urgent need for immediate antiarrhythmic treatment was thus strikingly demonstrated.

Difficulties in the differential diagnosis of atrial tachycardia and flutter have been discussed by several workers. Simonson and Berman[65] studied 10 patients with atrial rates of 158 to 400 per minute and various degrees of atrioventricular block. Utilizing as criteria the isoelectric intervals, the atrial rates and the response to carotid-sinus stimulation, they found no basis for a clear-cut differentiation of tachycardia and flutter. A similar dilemma was encountered in the case reported by Smelin et al.[66] After reviewing numerous clinical records and investigating the problem experimentally, it was concluded[11] that the commonly accepted criteria for an electrocardiographic diagnosis of flutter are confusing and often meaningless. These criteria were criticized as follows:

> The atrial rate must be 250 or more beats per minute. Patients often present rates varying spontaneously from 200 to 300 in the same tracing. Moreover, when quinidine is given to patients with rates over 250, a gradual slowing of the rate occurs before normal sinus rhythm is restored. If a diagnosis of flutter required rates of 250 or more, these patients would have both "flutter and "tachycardia" within a brief period.
>
> Baseline must present continuous undulations or a pure sine-wave pattern. The undulations in electrocardiograms of flutter have been attributed to the presence of atrial repolarization (Ta) waves, which may also appear in some cases of tachycardia. Whether or not a pure undulatory or sine-wave pattern occurred was found to depend largely on the atrial rate, on previous medication and on the relation of the electrodes to the atrium. This pattern was recorded as a rule only in extremely rapid flutter or after the administration of drugs such as quinidine. Continuous undulations in all leads were observed in only about 5 per cent of tracings diagnosed as flutter. Furthermore, a sine-wave contour was often present in some leads and absent in simultaneously recorded leads that were otherwise identical. Thus, if a pure undulation or sine-wave pattern were essential for a diagnosis of flutter, most cases would be overlooked. Many of the remaining patients would exhibit "flutter" in some leads and "tachycardia" in others.
>
> Atrioventricular block must be present. The presence or absence of block was found to depend not on a difference in mechanism of the atrial arrhythmia but rather on the efficiency of the atrioventricular-conduction system. This criterion for the differentiation of atrial tachycardia and flutter was therefore considered inadequate and artificial.

These observations were regarded as proof that no physiologic basis exists for distinguishing between atrial tachycardia with block and flutter. Furthermore, the common practice of designating an arrhythmia as "flutter" or "tachycardia" was criticized because it fails to indicate what is actually happening in the atria. A proposal was made to classify as variants of supraventricular tachycardia all arrhythmias now diagnosed as either atrial tachycardia or flutter. This diagnostic term was to be supplemented by a physiologic description including the atrial rate, the configuration of the atrial deflection and the site of the ectopic focus. Any abnormalities in atrioventricular conduction or in the ventricular complex were also to be described.

Recent clinical reports concerning atrial fibrillation include a phonographic study of the intensity of the first heart sound.[67] Rytand[68] noted that the absence of variable accentuation of the first heart sound in fibrillation was strong evidence of mitral stenosis. The diagnosis could often be made despite the absence of a typical murmur. Several groups of investigators[69-72] utilized new technics of studying hemodynamics to determine the desirability of converting fibrillation to normal sinus rhythm. A significant increase in cardiac output during exercise was consistently demonstrated after conversion. Only one group,[71] however, noted a striking increase in resting cardiac output after sinus rhythm had been restored. Other cardiovascular adjustments observed after conversion included a decrease in pulmonary blood flow, a fall in mean pulmonary arterial pressure, improvement in the rate of systemic blood flow as determined by mean circulation time, a rise in oxygen extraction after exercise and a return to normal of the atrioventricular oxygen difference. These changes alone are sufficient to justify conversion of fibrillation to sinus rhythm in selected cases. In addition prevention of embolization from the fibrillating atrium constitutes a definite indication for conversion in certain patients.

Wolff[73] emphasized the point that fibrillation may be the earliest manifestation of pulmonary embolism, preceding by days any other clinical evidence of the embolic incident. He points out that the onset of fibrillation followed by pain in the chest usually signifies pulmonary embolism. Chest pain followed by fibrillation often indicates myocardial infarction. The possibility of pulmonary embolism should al-

ways be considered in patients presenting paroxysmal atrial fibrillation of unexplained origin.

In the evaluation of operations for mitral stenosis the preoperative presence of atrial fibrillation was found to have no adverse effect on the results.[74] When sinus rhythm prevailed before mitral commissurotomy, fibrillation was a common postoperative development. The fibrillation appearing after operation was frequently difficult or impossible to convert to sinus rhythm.

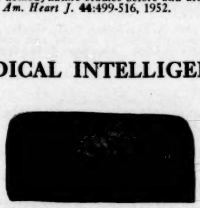
(To be concluded)

References

1. Linenthal, A. J., and Freedberg, A. S. Measures used in prevention and treatment of cardiac arrhythmias. *New Eng. J. Med.* **241**: 570-578 and 612-620, 1949.
2. Lewis, T. *The Mechanism and Graphic Registration of the Heart Beat.* Third edition. 529 pp. London: Shaw and Sons, Ltd., 1925.
3. Mines, G. R. On circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation. *Tr. Roy. Soc. Canada* **8** Sect. IV: 43-52, 1914.
4. Lewis, T., Feil, H. S., and Stroud, W. D. Observations upon flutter and fibrillation. II. Nature of auricular flutter. *Heart* **7**:191-245, 1920.
5. Lewis, T., Drury, A. N., and Iliescu, C. C. Demonstration of circus movement in clinical flutter of auricles. *Heart* **8**:341-359, 1921.
6. Prinzmetal, M., Goldman, A., Gerlach, E., and Kennamer, R. Nature of spontaneous auricular flutter in man as shown by direct observation during cardiac surgery. *J. A. M. A.* (in press).
7. Cabrera Cosio, E., and Sodi Pallares, D. Discussión del movimiento circular y prueba directa de su existencia en el flutter auricular clínico. *Arch. Inst. cardiol. México* **17**:850-869, 1947.
8. Sodi Pallares, D. Personal communication.
9. Prinzmetal, M., et al. Auricular flutter. *Am. J. Med.* **11**:410-430, 1951.
10. Hecht, H. H. Mechanism of auricular fibrillation and flutter. *Circulation* **7**:594-606, 1953.
11. Prinzmetal, M., et al. *The Auricular Arrhythmias.* 387 pp. Springfield, Illinois: Charles C Thomas, 1952.
12. Scherf, D. Studies on auricular tachycardia caused by aconitine administration. *Proc. Soc. Exper. Biol. & Med.* **64**:233-239, 1947.
13. Rosenblueth, A., and Garcia Ramos, J. Studies on flutter and fibrillation. II. Influence of artificial obstacles on experimental auricular flutter. *Am. Heart J.* **33**:677-684, 1947.
14. Garcia Ramos, J., and Rosenblueth, A. Estudios sobre el flutter y la fibrilación. III. La actividad autosostenida en el musculo aislado del mamifero. *Arch. Inst. cardiol. México* **17**:302-336, 1947.
15. Rosenblueth, A., and Garcia Ramos, J. Estudios sobre el flutter y la fibrilación. IV. La naturaleza del flutter auricular y de la actividad lenta autosostenida del musculo auricular aislado. *Arch. Inst. cardiol. México* **17**:441-457, 1947.
16. Scherf, D., Romano, F. J., and Terranova, R. Experimental studies on auricular flutter and auricular fibrillation. *Am. Heart J.* **36**: 241-251, 1948.
17. Scherf, D., Scharf, M. M., and Gokten, M. F. Effect of stretch and pressure on stimulus formation in dog's auricle. *Proc. Soc. Exper. Biol. & Med.* **70**:708-711, 1949.
18. Scherf, D., and Terranova, R. Mechanism of auricular flutter and fibrillation. *Am. J. Physiol.* **159**:137-142, 1949.
19. Scherf, D., Morgenbesser, L. J., Nightingale, E. J., and Schaeffeler, K. T. Further studies on mechanism of auricular fibrillation. *Proc. Soc. Exper. Biol. & Med.* **73**:650-654, 1950.
20. Scherf, D. Mechanism of flutter and fibrillation. *Bull. New Eng. M. Center* **13**:97-101, 1951.
21. Wilson, F. N. Personal communication.
22. Katz, L. N., and Pick, A. Mechanism of auricular flutter and auricular fibrillation. *Circulation* **7**:601-606, 1953.
23. Dawes, G. S. Experimental cardiac arrhythmias and quinidine-like drugs. *Pharmacol. Rev.* **4**:43-84, 1952.
24. Brown, B. B., and Acheson, G. H. Influence of procaine and some related compounds upon experimental auricular flutter in dog. *J. Pharmacol. & Exper. Therap.* **102**:200-207, 1951.
25. Brown, B. B. Study of factors related to effects of quinidine in experimental auricular flutter. *Circulation* **5**:864-869, 1952.
26. Scherf, D., Schaffer, A. I., and Blumenfeld, S. Mechanism of flutter and fibrillation. *Arch. Int. Med.* **91**:333-352, 1953.
27. Lewis, T. Observations upon flutter and fibrillation. IX. Nature of auricular fibrillation as it occurs in patients. *Heart* **8**:193-227, 1921.
27a. Lewis, T., Drury, A. N., and Iliescu, C. C. Demonstration of circus movement in clinical fibrillation of auricles. *Heart* **8**:361-389, 1921.
28. Prinzmetal, M., et al. Auricular fibrillation. *J. A. M. A.* **146**: 1275-1281, 1951.
29. Groedel, F. M., and Miller, M. Auricular flutter studied in direct leads from human heart. *J. Appl. Physiol.* **3**:183-188, 1950.
30. Lewis, T. Paroxysmal tachycardia, result of ectopic impulse formation. *Heart* **1**:262-282, 1910.
31. Barker, P. S., Wilson, F. N., and Johnston, F. D. Mechanism of auricular paroxysmal tachycardia. *Am. Heart J.* **26**:435-445, 1943.
32. Trendelenburg, W. Untersuchungen über des Verhalten des Herzmuskels bei rythmischer elektrischer Reizung. *Arch. f. Anat. u. Physiol.* (Physiol. Abt.) 271-310, 1903.
33. Rothberger, C. J., and Winterberg, H. Das Flimmern der Herzkammern. (Weiterer Beitrag zur Pathogenese des Flimmerns.) *Ztschr. f. d. ges. exper. med.* **4**:407-426, 1916.
34. Lewis, T. Observations upon curious and not uncommon form of extreme acceleration of auricle: "auricular flutter." *Heart* **4**: 171-220, 1912.
35. Lown, B., Wyatt, N. F., Crocker, A. T., Goodale, W. T., and Levine, S. A. Interrelationship of digitalis and potassium in auricular tachycardia with block. *Am. Heart J.* **45**:589-601, 1953.
36. Cunningham, G. C., and Schnitzker, W. F. Use of neo-synephrine in paroxysmal supraventricular tachycardia. *J. Pediat.* **37**:727-732, 1950.
37. Sokolow, N. Personal communication.
38. Scherf, D., Blumenfeld, S., Mueller, P., and Beinfield, W. H. On response of ectopic auricular tachycardias to vagus stimulation. *Am. Heart J.* **45**:95-107, 1953.
39. Blumgart, H. L., et al. Nature of auricular fibrillation and flutter: symposium. *Circulation* **7**:591-593, 1953.
40. Rosenblueth, A. Mechanism of auricular flutter and auricular fibrillation. *Circulation* **7**:612, 1953.
41. Prinzmetal, M. Mechanism of spontaneous auricular flutter and fibrillation in man. *Circulation* **7**:607-611, 1953.
42. Katz, L. N., and Pick, A. Mechanism of auricular flutter and auricular fibrillation. *Circulation* **7**:601-606, 1953.
42a. Michel, J., et al. Arrhythmias during intracardiac catheterization. *Circulation* **2**:240-244, 1950.
43. Fowler, N. O., Westcott, R. N., and Scott, R. C. Disturbances in cardiac mechanism of several hours' duration complicating cardiac venous catheterization. *Am. Heart J.* **42**:652-660, 1951.
44. Stevenson, I. P., Duncan, C. H., Wolf, S., Ripley, H. S., and Wolff, H. G. Symposium on cardiovascular diseases: life situations, emotions, and extrasystoles. *Psychosom. Med.* **11**:257-272, 1949.
45. Duncan, C. H., and Stevenson, I. Paroxysmal arrhythmias: psychosomatic study. *Geriatrics* **5**:259-267, 1953.
46. Altschule, M. D. Emotion and circulation. *Circulation* **3**:444-454, 1951.
47. Szekely, P., and Snaith, L. Paroxysmal tachycardia in pregnancy. *Brit. Heart J.* **15**:195-198, 1953.
48. Cole, S. L. Digitalis intoxication: chronic effects manifested by diarrhea and auricular flutter. *Am. Heart J.* **39**:900-903, 1950.
49. Weinberg, S. L., and Schoenwetter, A. H. Auricular flutter and indirect cardiac trauma. *Arch. Int. Med.* **88**:252-257, 1951.
50. Bortin, M. M., Silver, S., and Yohalem, S. B. Diagnosis of masked hyperthyroidism in cardiac patients with auricular fibrillation. *Am. J. Med.* **11**:40-43, 1951.
51. Kissane, R. W., Brooks, R., and Clark, T. E. Relation of supraventricular paroxysmal tachycardia to heart disease and basal metabolism rate. *Circulation* **1**:950, 1950.
52. Griffin, W. R., Nelson, H. G., and Seal, J. R. Hemochromatosis with auricular fibrillation: case report. *Am. Heart J.* **39**:904-908, 1950.
53. Levin, E. B., and Golum, A. Heart in hemochromatosis. *Am. Heart J.* **45**:277-288, 1953.
54. Fox, T. T., Weaver, J., and March, H. W. On mechanism of arrhythmias in aberrant atrioventricular conduction (Wolff-Parkinson-White). *Am. Heart J.* **43**:507-520, 1952.
55. Prinzmetal, M., et al. *Accelerated Conduction, The Wolff-Parkinson-White Syndrome and Related Conditions.* 110 pp. New York: Grune and Stratton, 1952.
56. Lian, C., Cassimatis and Hébert. Intérêt de la dérivation précordiale auriculaire S5 dans le diagnostic des troubles du rythme auriculaire. *Arch. d. mal. du coeur* **45**:481-489, 1952.
57. Nadas, A. S., Daeschner, C. W., Roth, A., and Blumenthal, S. L. Paroxysmal tachycardia in infants and children: study of 41 cases. *Pediatrics* **9**:167-181, 1952.
58. Silverman, J. J., and Werner, M. Fatal paroxysmal tachycardia in newborn infant with Wolff-Parkinson-White syndrome. *J. Pediat.* **37**:765-773, 1950.
59. Silverman, J. J., and Race, O. M. Paroxysmal tachycardia with ventricular rate of 365 per minute. *Am. Heart J.* **37**:1139-1143, 1949.
60. Hay, J. D., and Keidan, S. E. Persistent ectopic auricular tachycardia in children. *Brit. Heart J.* **14**:345-349, 1952.
61. Prinzmetal, M., and Goldblatt, H. Personal observation.
62. Leach, E. M., and Gibson, S. Auricular flutter in infancy. *Am. J. Dis. Child.* **80**:606-609, 1950.
63. Askey, J. M. Auricular paroxysmal tachycardia in association with myocardial infarction. *Am. Heart J.* **37**:425-434, 1949.
64. *Idem.* Auricular flutter in association with myocardial infarction. *Am. J. Med.* **6**:453-461, 1949.
65. Simonson, E., and Berman, R. Differentiation between paroxysmal auricular tachycardia with partial A-V block and auricular flutter. *Am. Heart J.* **42**:387-398, 1951.
66. Smelin, A., Burstein, J., Blinder, H., and Lubart, A. Tachycardia and spontaneous flutter in adult: report of case with rate of 300 and 1:1 flutter. *Arch. Int. Med.* **91**:685-690, 1953.

67. Ravin, A., and Bershof, E. Intensity of first heart sound in auricular fibrillation with mitral stenosis. *Am. Heart J.* **41**:539-548, 1951.
68. Rytand, D. A. Variable loudness of first heart sound in auricular fibrillation. *Am. Heart J.* **37**:187-204, 1949.
69. Hecht, H. H., Osher, W. J., and Samuels, A. J. Cardiovascular adjustments in subjects with organic heart disease before and after conversion of atrial fibrillation to normal sinus rhythm. *J. Clin. Investigation* **30**:647, 1951.
70. Hansen, W. R., McClendon, R. L., and Kinsman, J. M. Auricular fibrillation: hemodynamic studies before and after conversion with quinidine. *Am. Heart J.* **44**:499-516, 1952.
71. Kory, R. C., and Meneely, G. R. Cardiac output in auricular fibrillation with observations on effects of conversion to normal sinus rhythm. *J. Clin. Investigation* **30**:653, 1951.
72. Wegria, R., et al. Effect of auricular fibrillation on cardiac output, coronary blood flow and mean arterial blood pressure. *Am. J. Physiol.* **163**:135-140, 1950.
73. Wolff, L. Pulmonary embolism. *Circulation* **6**:768-776, 1952.
74. Janton, O. H., Glover, R. P., O'Neill, T. J. E., Gregory, J. E., and Froio, G. F. Results of surgical treatment for mitral stenosis: analysis of one hundred consecutive cases. *Circulation* **6**:321-333, 1952.

MEDICAL INTELLIGENCE



PRIMARY CHYLOPERICARDIUM*

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EFFUSION of chyle into various body cavities is an interesting and uncommon clinical phenomenon. In spite of its infrequent occurrence the management of chylous effusion has stimulated a number of excellent articles.[1-3] Since the greatest portion of the chyle vascular system courses through the chest via the thoracic duct it is not surprising that chyle most often extravasates into the pleural cavities.

Chylopericardium is particularly uncommon; we have found only 6 case reports in which chyle appeared in the pericardial sac, and in each there was associated massive chylothorax.[1, 4, 5] Primary chylopericardium unrelated to trauma must be of unusual rarity; we have not found any reference to such an entity. Experience with a patient who presented primary chylopericardium prompts us to report the case in detail; we believe that the diagnostic features in the surgical therapy may be helpful in future cases.

CASE REPORT

The patient was a 31-year-old housewife and the mother of 4 normal children. The past history and review of the systems were noncontributory. Nine months earlier she had complained of "dizzy spells" and had sought medical attention. The initial examination was said to have been negative. The dizzy spells continued, and 1 month after onset she complained of dyspnea and choking sensations. Dyspnea became the outstanding symptom and progressed to such an extent that hospitalization and oxygen therapy were required on more than one occasion. Although the details are not known it was recognized that the patient had a pericardial effusion, and on 2 occasions needle aspiration demonstrated a milky pericardial fluid. The patient was treated with digitalis, sedatives, diuretics and a course of cortisone therapy without significant change in her condition. Cultures made from the pericardial fluid were reported as showing no growth. She was transferred to the Cleveland Clinic Hospital on December 9, 1952. At this time she slept in an almost erect sitting position because of the severe dyspnea.

Physical examination disclosed a thin, asthenic woman with a blood pressure of 105/80. The pulse rate was 88 per minute, with a normal sinus rhythm. The significant findings consisted of engorged neck veins aggravated in the supine position, an enlarged liver palpable 3 cm. below the costal margin without pulsation and marked enlargement of the cardiac silhouette. Fluoroscopic study revealed tremendous cardiac enlargement, with almost complete absence of pulsations in the aorta and left cardiac border. The angle between the right cardiac border and the diaphragm was well preserved. The transverse cardiac diameter was 21 cm. (Fig. 1*A*).

Examination of the blood showed a red-cell count of 5,000,000, with a hemoglobin of 13.4 gm. per 100 cc., and a white-cell count of 3850, with 66 per cent neutrophils, 26 per cent lymphocytes, 2 per cent eosinophils and 5 per cent monocytes. The icteric index was 4. Urinalysis was negative, and urine culture was sterile. Serologic tests were repeatedly negative, as were other procedures, including the L.E. (plasma-dog) and tuberculin skin tests. The sedimentation rate was 0.85 mm. per minute, and the serum polysaccharides were 122 mg. per 100 cc. An electrocardiogram demonstrated a sinus rhythm, with low voltage QRS complexes in the limb leads, and was regarded as consistent with myocardial changes with question of digitalis effect.

A pericardial tap was performed, 60 cc. of milky fluid being removed. Subsequent study revealed that the fluid contained no tumor cells; the specific gravity was 1.018 and the protein content was 3.15 gm. per 100 cc. There were 800 red blood cells and 600 white blood cells per cubic millimeter; virtually all the white cells were lymphocytes. The cholesterol content was 133 mg. per 100 cc. No cholesterol crystals were seen on the smears. Routine and tuberculous cultures were subsequently reported as negative.

The initial clinical impression was that of chronic pericarditis with effusion; whereas the gross appearance of the effusion suggested chyle this observation was disregarded. On December 15 an exploratory operation was performed through a left subpectoral intercostal incision. The pericardial sac was enlarged and distended, but only slightly thickened, with no evidence of inflammatory reaction. Incision of the pericardium resulted in extrusion under pressure of 1 liter or more of milky fluid. A biopsy disk of pericardium was excised, a window approximately 4 cm. in diameter being left, to create a pericardial pleural fistula with the left hemithorax. After evacuation of the pericardial fluid the heart seemed only moderately enlarged, and the epicardium was coated with a thin milky film. There was no evidence of neoplasm, tubercles or other striking pathologic conditions. At the time of operation the surgeon believed that an unusual form of tuberculous pericarditis was the most likely diagnosis, and it was decided to give the patient streptomycin therapy for 3 to 6 months.

Roentgenograms after operation showed a dramatic change (Fig. 1*B*), and the patient was symptomatically improved. Two weeks later she was discharged from the hospital; the chest appeared normal on physical and roentgenographic examination.

Histologic study of the pericardial biopsy disclosed a slight, nonspecific inflammation. Fluid and tissue cultures were sterile.

On March 4, 1953, approximately 3 months after discharge, the patient returned for re-examination. The vertigo and dyspnea had promptly recurred. Fluoroscopic study revealed massive pericardial effusion (Fig. 2*A*). The patient was readmitted to the hospital for additional studies.

A pericardial tap was productive of the same type of milky fluid as had been observed on previous occasions. Whereas it had been noted that the clinical appearance was typical of

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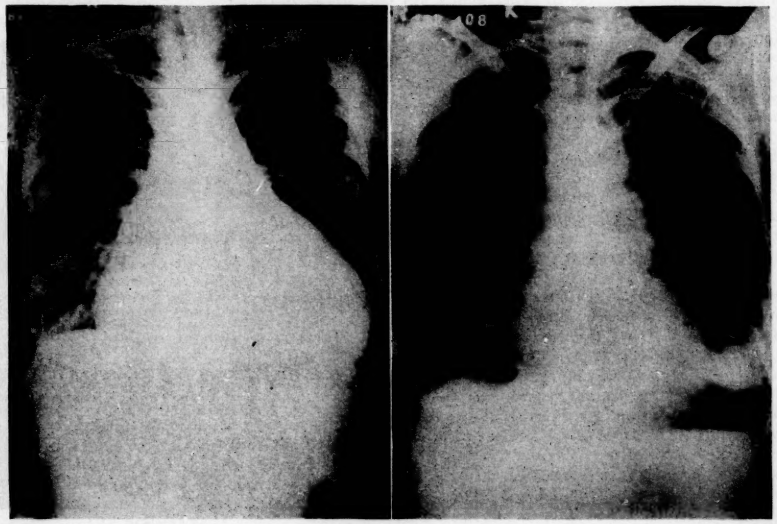
chyle little significance had been attached to this obvious and simple finding. The fluid contained about 800 white cells per cubic millimeter; 95 per cent of the cells were lymphocytes, and the fluid cleared upon the addition of ether. At this time the serum fat and lipids were carefully studied and were found to be within normal limits. The fat studies on the pericardial fluid were typical of chyle.

The 1st effort was then made to demonstrate a communication between the pericardial sac and the thoracic duct. On the basis of several reports[6, 7] an effort was made to give a tracer substance orally that might later be detected in the pericardial fluid. The test proved to be simple and conclusive.

resembled lymph but did not have the milky appearance of the pericardial fluid. The right side of the pericardial sac was opened widely, and a large window created for evacuation and inspection. Direct communication between the pericardial sac and the thoracic duct or the cystic tumor mass could not be definitely established. The esophagus was then mobilized from the posterior mediastinum, and an apparently normal thoracic duct was identified at the level of the 10th thoracic vertebra, where it appeared as a single structure. The duct was then ligated in continuity with fine-silk sutures. A large portion of the cystic tumor was dissected free from the anterior mediastinum and removed for histologic examination. The large pericardial window was



A B

FIGURE 1. *Roentgenograms Taken at the Time the Patient Was First Seen* (A), *Demonstrating the Enormous Cardiac Silhouette and the Total Absence of Any Pleural Effusion on Either Side* (*Note That There Is Nothing to Suggest Widening of the Superior Mediastinum*), *and after the First Operative Procedure* (B), *Showing the Pleural Reaction at the Left Base Secondary to the Drainage of Chyle from the Pericardium into This Area.*

A pericardial tap was performed on the day before the test, 150 cc. of fluid being removed to reduce the pericardial tension. On the following morning the patient was given 20 mg. of Sudan III dissolved in an emulsion of corn oil and milk. A pericardial tap was performed 4½ hours later; 300 cc. of fluid was removed. The aspirated fluid was pink, but the color was thought to be due to the presence of blood. Careful extraction of fat with ether and evaporation to virtually complete dryness was necessary to demonstrate the presence of the dye in the pericardial fluid. Although the test seemed conclusive it was repeated on the following day. The same amount of Sudan III dissolved in olive oil and milk was given, and 125 cc. of fluid aspirated from the pericardium 8 hours later. Again, extraction of the fat and the evaporation showed sufficient dye to establish the presence of a communication between the thoracic duct and the pericardial sac.

On March 16 a 2d operative procedure, a formal thoracotomy on the right, was performed. When the chest was opened a soft, multicystic tumor mass was observed in the superior mediastinum. This extended down the posterior gutter to the hilus of the lung. Needle aspiration of the cystic areas produced fluid that grossly

sutured open so that all drainage would be directed into the right pleural space. The chest was closed with 2 catheters to continuous waterseal drainage.

The postoperative course was benign. Two weeks after operation x-ray study of the chest was practically negative (Fig. 2*B*). There has been no reaccumulation of pericardial effusion in the 6 months since operation.

The histologic diagnosis of the cystic tumor mass was mediastinal hygroma (lymphangiomatous hamartoma). Microscopical examination revealed large endothelial-lined spaces containing a granular coagulum separated by loose stroma and focal lymphocytes (Fig. 3).

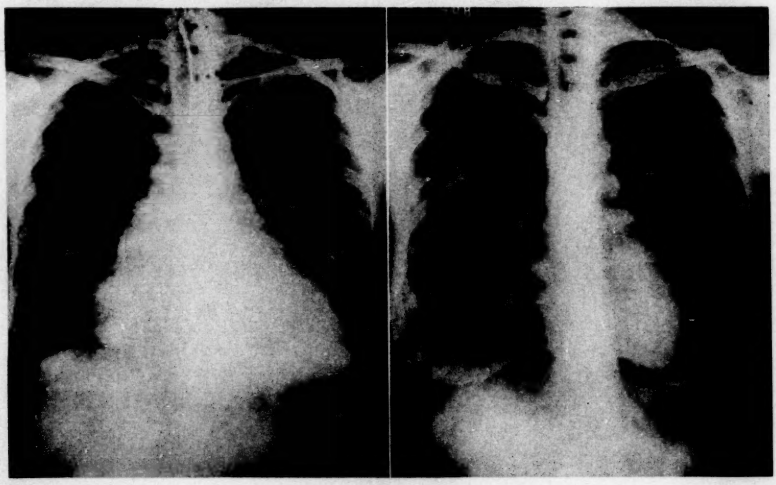
DISCUSSION

The commonest cause of spontaneous chylous effusion is a malignant neoplasm, of which the retroperitoneal and posterior mediastinal lymphoblastoma has been most frequently designated. Yater,[1] in his extensive review, lists the following other

causes: tuberculosis, thrombosis of the superior vena caval system, lymphangiectasis, polyserositis and cirrhosis. To this list must be added lymphangioma or cystic hygroma on the basis of the case reported above, and 2 other case reports by Swift and Neuhof[8] and Touroff and Seley.[9] From the case reported above, an anatomic communication between the thoracic-duct system and the pericardium seems likely when an associated congenital lesion such as a mediastinal hygroma is present.

communication seems more likely. Whether this is the correct explanation in the case presented above cannot be stated with certainty; nevertheless, such a communication undoubtedly existed and was interrupted by the ligation of the thoracic duct below this point.

In retrospect the fluid should certainly have been recognized as chyle from the outset. However, it seemed inconceivable at that time that such a massive chylous pericardial effusion was possible,



A B

FIGURE 2. *Roentgenograms before* (A) *and Six Months after* (B) *the Operation, Showing the Massive Recurrence of Chylopericardium. The pleuropericardial window into the left side of the chest has obviously sealed* (A), *since no pleural effusion is evident. After operation* (B) *the cardiac silhouette is normal and there is no significant pleural reaction or effusion. The thoracotomy was performed through the right sixth intercostal space with resection of short posterior segments of the adjacent sixth and seventh ribs to give additional exposure.*

Whereas the anatomy of the thoracic-duct system has been extensively studied, the lymphatic drainage of the pericardium and the potential relation with that system have not been emphasized; that there is some relation between the lymphatic drainage of the posterior pericardial sac and the thoracic-duct system has been suggested by observations in the surgical treatment of carcinoma of the esophagus, in which dilated lymphatic channels have occasionally been encountered reaching from the posterior pericardium to the vicinity of the thoracic duct. When the additional factor of a congenital hygromatous lesion presumably involving the thoracic duct is also present, the possibility of a reflux of chyle into the pericardium through such a

and there was nothing to suggest neoplasm on x-ray study. Best and Taylor[10] stated that in the dog an obstructed thoracic duct will build up a pressure equivalent to 15 cm. of water. In the case presented above, chyle must have passed into the pericardium under at least this amount of pressure because the immense enlargement of the pericardial sac demonstrated that it was subjected to a significant amount of pressure over a long period, and the patient certainly manifested symptoms of cardiac tamponade. We are unable to state definitely whether the actual communication was through a dilated normal lymphatic channel or through the tumor into which the thoracic duct presumably drained. Thus, we are unable to predict whether isolated chylopericardium

could be caused by simple high obstruction of the thoracic duct.

We wish to emphasize the value of the use of lipophilic dyes in the study of extravasation of chyle. Sudan III, as used in this case, does not yield an intense color, and the detection of its presence requires extraction of the fat with ether and evaporation to concentrate the dye.

FIGURE 3. *Photomicrograph of a Typical Section of the Tumor. This is considered characteristic of a cystic hygroma showing large endothelial-lined spaces separated by a loose fibrous stroma containing focal areas of lymphocytes.*

We believe that the tumor in this patient has no significant growth potential and that the patient has no significant underlying heart disease; therefore, the long-term prognosis should be excellent.

SUMMARY

A case of a hitherto undescribed clinical entity, primary chylopericardium, is reported. After ligation of the thoracic duct low in the chest recovery was apparently complete.

REFERENCES

1. Yater, W. M. Non-traumatic chylothorax and chylopericardium: review and report of case due to carcinomatous thromboangiitis obliterans of thoracic duct and upper great veins. *Ann. Int. Med.* 9:600-616, 1935.
2. Lampson, R. S. Traumatic chylothorax: review of literature and report of case treated by mediastinal ligation of thoracic duct. *J. Thoracic Surg.* 17:778-791, 1948.
3. Meade, R. H., Jr., Head, J. R., and Moen, C. W. Management of chylothorax. *J. Thoracic Surg.* 19:709-723, 1950.
4. Andrews, C. F. Traumatic intrathoracic rupture of thoracic duct with chylothorax. *Nebraska M. J.* 14:26-29, 1929.
5. Scannell, J. G. Discussion of Meade et al.[3] P. 720.
6. Auld, W. H. R., and Needham, C. D. Experiments on fat absorption in case of chylothorax. *Lancet* 1:991-993, 1951.
7. Klepser, R. G. Discussion of Meade et al.[3] P. 722.
8. Swift, E. A., and Neuhof, H. Cervicomediastinal lymphangioma with chylothorax. *J. Thoracic Surg.* 15:173-181, 1946.
9. Touroff, A. S. W., and Seley, G. P. Chronic chylothorax associated with hygroma of mediastinum. *J. Thoracic Surg.* 26:318-320, 1953.
10. Best, C. H., and Taylor, N. B. *The Physiological Basis of Medical Practice: A text in applied physiology.* Fifth edition. 1330 pp. Baltimore: Williams & Wilkins, 1950. P. 34.

BY THE LONDON POST

Doctors and the Press — Mass Medication — Smoking and Carcinoma

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AN eminent English physician told me how he once delivered a paper at the annual meeting of the Young Turks in Atlantic City. To his consternation and to the embarrassment of his American hosts, a full report appeared in the evening newspaper. He assured his friends that he had held no press conference and had spoken to no one outside the medical profession since reading his paper. He told them that he had gone straight from the meeting to the Chalfont Haddon Hotel, where the only stranger he had spoken to was a good-looking woman medical student, who had approached him in the lounge, expressed interest in his subject and asked him to clarify a few points. As he related this, his friends smiled and explained, "She was no medical student — she was a newspaper woman!"

The relation between the medical profession and the press was recently discussed in the *British Medical Journal*. Professor Ian Aird pointed out in a letter that although physicians have tried to hold to the rule that medical information should only be communicated through a scientific journal, the lay press considers it legitimate to collect medical news by any available means, any method being legitimate and honorable. His letter was prompted by a personal experience at the time he performed a widely publicized operation on Siamese twins. Windows at the hospital had to be blacked out to restrain aggressive press photographers, and he himself had to call the police to clear the precincts of his home of an unruly crowd of reporters. It is not surprising that the newspaper reports about the operation and the progress of the patients contained many inaccuracies, which had to be corrected by a statement from the Press Association. Professor Aird points out that premature publicity and distorting headlines may be most disturbing to both patients and their relatives. The patient awaiting treatment by new technics may be dismayed, and at times the relatives may be subjected to an unfair degree of press interest. Furthermore, the full glare of publicity does not make it easy for a surgeon to decide to undertake a dangerous operation.

Although Professor Aird's own case is an extreme example, he stresses the fact that the problem must be faced. Because the press is no longer content to await the presentation of medical facts in the medical journals, he suggests that anonymity and accuracy might be ensured if news were given through a public-relations officer. Commenting

on the subject, the *British Medical Journal* emphasizes the point that the doctor's first and last concern is clearly to protect the interests of his patients and their relatives. It doubts whether the system of a public-relations officer would be satisfactory and suggests that the answer may be better relations between the doctors and the press. From Professor Aird's experience, it seems that this might be a difficult exercise in personal relations.

* * *

A remarkable debate took place in the House of Lords last month when a speaker asserted that mass medication, such as the addition of chalk to flour, iodine to salt and fluorine to public water supplies, was an infringement of the liberty of the subject. He claimed that the dose was administered without regard for age, sex or physical condition and irrespective of whether it was required or not. Such mass medication was an offense against the basic code of medical practice. Lord Amulree denied that there was any negation of medical practice and said that a doctor did not exist primarily to cure his patients but to stop them from becoming sick. He assured the House that chlorination does not harm the water supply and explained that calcium insufficiency could be prevented by the addition of chalk to flour. Similarly, if the addition of controlled quantities of iodine to salt helped reduce the incidence of goiter, he could see no objection to such an addition.

Lord Webb Johnson also protested against the suggestion that mass medication was contrary to the ethics and traditions of the medical profession. He recalled that he had seen George Crile, of Cleveland, Ohio, who showed that goiters were related to a deficiency of iodine and urged that artificial means used to correct the deficiency, operate on 20 goiters in a morning. Today, although Cleveland is an area of endemic goiter, the population has an adequate iodine intake through iodized water supplies and canned vegetables grown outside the area. As a result, George Crile, Jr., on a recent visit to England, was able to say that he now only operates on one or two goiters a day. In conclusion, Lord Webb Johnson stressed the fact that the addition of iodine to water is not mass medication, but rather a reinforcement of nature's own supply.

Replying for the Government, the Parliamentary Secretary to the Ministry of Agriculture explained that if it had not been for the addition of calcium to flour, the national average intake in the first half of 1952 would have been 10 per cent below the estimated daily requirements of 0.8 gm. per day for adults. Concerning iodine, the Medical Research Council committee on thyroid diseases had reported in 1948 that goiter was apparently on the increase and recommended the addition of iodine to domestic salt. Finally, the fluoridation of water supplies was the only measure with any promise of reducing the incidence of dental caries, and on this matter the Minister of Health had accepted the recommendation of the medical mission that had visited the United States. He pointed out that the Government had a general responsibility for ensuring the health of the people and would be failing in its duty if it did not take the action that had been described as mass medication when an overwhelming case had been made out on scientific grounds for such practical public-health measures.

* * *

Tobacco shares fell sharply when the Minister of Health made an official announcement that a relation has been established between smoking and carcinoma of the lung. He urged that alarmist conclusions should not be drawn from this information, which was contained in a report by the Standing Advisory Committee on Cancer and Radiotherapy. As the *Times* points out, the Minister's statement called attention to a problem of intense public interest. In 1952 there were 87,642 deaths from cancer in England and Wales, and 14,218 of these were due to carcinoma of the lung. Further analysis shows that this disease is responsible for 26 per cent of all cancer deaths in males and for nearly 5 per cent of deaths from all causes in males. In 1931 only 1880 deaths were reported as due to carcinoma of the lung in England and Wales, representing 5 per cent of all cancer deaths and 0.5 per cent of deaths from all causes in males.

No convincing explanation has been produced for the increase, although in 1952 Professor Bradford Hill concluded that "the association between smoking and cancer of the lung is real." On the other hand more facts are needed for a final judgment. Thus, the presence of a carcinogenic agent in tobacco is uncertain; cigarette smokers are more prone than pipe smokers, and the importance of atmospheric pollution requires investigation. Meanwhile, the tobacco firms have offered the handsome sum of £250,000 to the Medical Research Council for research purposes into the etiology of the condition; for the time being, young people must be advised of the danger of oversmoking and the general motto must continue to be "moderation in all things."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

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CASE 40121*

PRESENTATION OF CASE

A six-year-old Negro boy was admitted to the hospital because of abdominal pain and vomiting.

The patient became ill one month before admission with high fever, diarrhea and a skin rash chiefly involving the arms and legs, but there were a few lesions on the back. These lesions at first consisted of small, red papules and in about twelve hours had more the appearance of ringworm infection. The skin lesions, fever and diarrhea persisted for about three weeks, during which he had anorexia and lost a great deal of weight. His physician gave him penicillin for three days as well as some liquid medicine. He apparently recovered, played about the yard and generally seemed to be well except that he complained of feeling tired on several occasions. One episode of epistaxis occurred during this period. Four days before admission he began to complain of abdominal pain, which increased in intensity and was accompanied by vomiting. For about six weeks he had had intermittent interscapular pain as well as pain in the fingers.

The past history gave no pertinent information.

Physical examination showed a slightly dyspneic boy on his hands and knees, who appeared acutely ill and very anemic. The eyes, ears, nose, tongue and teeth were normal. The mucous membranes were pale. There was no lymphadenopathy, but the neck veins were markedly distended. There was slight dullness in the lower half of the lung fields, with normal breath sounds and no rales. The mediastinum was not widened. The point of maximum impulse was in the sixth intercostal space in the anterior axillary line. There was moderate enlargement of the right side of the heart. The heart rate was rapid and had a gallop type of rhythm with a continuous murmur at the apex. The pulmonic second sound was greatly accentuated. The liver edge was palpable at the level of the umbilicus and only mildly tender. There was no ascites and no peripheral edema.

*Discussed on February 8, 1951.

The temperature was 98.8°F., the pulse 140 to 150, and the respirations 48. The blood pressure was 80 systolic, (?) 60 diastolic.

The urine had a specific gravity of 1.025 and gave a ++ test for albumin; the sediment contained 6 to 8 white cells per high-power field and no red cells or casts. Examination of the blood disclosed a red-cell count of 3,410,000, with a hemoglobin of 7 gm. per 100 cc., and a white-cell count of 13,100, with 88 per cent neutrophils, 10 per cent lymphocytes and 2 per cent monocytes. A stool examination was negative. An x-ray film of the chest showed marked cardiomegaly, with pulmonary congestion and a questionable pleural effusion on the right. An electrocardiogram demonstrated sinus tachycardia. The T-wave changes in the ST segment in Lead 1 were somewhat suggestive of pericarditis. Otherwise, the record was normal.

Shortly after admission, because of the marked pallor, a 150-cc. transfusion was started, but apparently it made respirations even more difficult and was stopped after 45 cc. had been administered. The patient was digitalized. On the third hospital day he complained of right-lower-quadrant pain and upon examination of the abdomen, the liver was found to be down farther than previously and seemed to be extremely tender. He also complained of a lesser degree of pain in the left side of the neck and shoulder. On this day the urine had a specific gravity of 1.010 and gave a + test for albumin, and the sediment contained 2 or 3 white cells and frequent casts per high-power field. The hemoglobin was 9.5 gm. per 100 cc., the red-cell count 4,000,000, and the white-cell count 12,000, with 42 per cent neutrophils and 58 per cent lymphocytes. Throughout the hospital course the temperature showed irregular elevations to 99.6 and 99.8°F., with occasional spikes to 101.4°F. Salicylates were given but produced no change. On the fourteenth hospital day the hemoglobin was 7 gm., and the white-cell count 20,000, with 75 per cent neutrophils and 25 per cent lymphocytes. Three days later the urine had a specific gravity of 1.015, with a ++ test for albumin, and the sediment contained 12 to 15 white cells and a few casts per high-power field. On the following day there was pitting edema of the ankles and feet. Four days later a second electrocardiogram was normal. On the twenty-sixth hospital day, the patient had a generalized tonic-clonic convulsion, and vomited. These symptoms were relieved by intravenous administration of Sodium Amytal. At this time the lungs were full of rales, and the blood pressure was 110 systolic, 70 diastolic. The urine had a specific gravity of 1.020 and gave a ++++ test for albumin; the sediment contained 5 white cells, 3 red cells and many casts per high-power field. The hemoglobin was 11.5 gm. per 100 cc., the red-cell count 5,000,000, and the white-cell count 16,000, with 86 per cent neutrophils and 14 per cent lymphocytes.

A test for sickling was negative in seventy-two hours. A stool gave a ++++ test for occult blood. On the twenty-ninth hospital day an electrocardiogram revealed sinus tachycardia, hypertrophy of the left ventricle, digitalis effect and probable, generalized ischemia. A second roentgenogram of the chest failed to show any changes from the previous one. The respiratory distress increased, rales became more noticeable, the radial pulse was imperceptible at times, and the patient died on the thirty-third hospital day.

The blood pressures on the twenty-eighth to thirty-first hospital days ranged between 130 systolic, 90 diastolic, and 140 systolic, 100 diastolic. Additional laboratory studies during the hospital stay were blood Wassermann and Kline tests, spinal-fluid examination and blood culture, all of which were negative. Sedimentation rates on the sixth and twenty-second hospital days were 10 mm. and 2 mm. per hour respectively. The patient continued to complain of right-sided abdominal pain intermittently throughout the hospital course.

Differential Diagnosis

Dr. J. Howard Means: When I was at the Medical College of the State of South Carolina in the latter part of December, 1950, Dr. Kenneth Lynch, president of the college, took me to the clinicopathological conference. The conduct of the conference was different from ours in that the faculty had a chance to make a diagnosis only after the fourth-year students had stuck their necks out. When this case was presented I had a chance to make a diagnosis, but did not make the right one. No one on the faculty or among the guests made the right diagnosis either, but one of the fourth-year students did. I asked Dr. Lynch to lend me the protocol, the slides and the anatomic diagnoses since I should like to have the pathologist at the Massachusetts General Hospital act as clinician.

Dr. Benjamin Castleman*: This six-year-old boy's illness began a month before hospital entry, and death occurred after a month's stay in the hospital. If a child who has apparently been well, becomes ill and dies in two months, one first thinks of an infection. From the physical examination and the x-ray films it is evident that the heart was enlarged, and therefore in a child of six years I immediately think of rheumatic infection with rheumatic heart disease. I believe one can build up quite a good case for rheumatic infection. The illness began with fever and a rash that was peculiarly described as being suggestive of ringworm infection. Ringworm infection does not spread so fast; I wonder if it could have been a toxic rash or a rash related to erythema multiforme, which is sometimes associated with rheumatic infection. Other findings that fit with rheumatic infection are epistaxis, cardiac enlargement and what was described as a continuous murmur at the apex. I tried to find out from a cardiologist what a continuous murmur at the apex meant, but was unable to get a satisfactory answer. If the patient really had a continuous murmur at the apex, one would have to believe that he had both a systolic and a diastolic murmur and that he had mitral stenosis and insufficiency. That would go along with the accentuated pulmonic second sound and is in favor of rheumatic infection. The electrocardiogram showed pericarditis, which may also occur with rheumatic infection. With the enlargement of the liver and pleural effusion I should then have to assume that he had congestive heart failure as well. The abdominal pain that brought him into the hospital and that apparently remained present throughout the entire hospital course could be explained by chronic passive congestion of the liver, with distention of the capsule. There is also the nebulous condition, rheumatic peritonitis, to which the abdominal pain may have been due.

There are, however, a number of findings against a rheumatic infection; the most prominent is that the joints were not involved. In a child of six years who has rheumatic infection, one would expect to find swelling and redness of the joints; he had only pain in the fingers. Also, I cannot explain the positive guaiac test on the stools too well by a rheumatic infection. Diarrhea and vomiting are as a rule not seen in rheumatic infection. The findings in the urine do not fit at all with rheumatic infection. There was a ++++ test for albumin, with casts, white cells and, toward the end, red cells in the sediment. To explain them, I should have to assume that in addition to the rheumatic infection, he had a true glomerulonephritis. Salicylates did not produce any improvement. Then, too, the fact that he was anemic does not fit with an acute rheumatic infection but is evidence that a more chronic disease may have been present.

One could postulate that he had a bacterial endocarditis superimposed on the rheumatic infection, but he had no petechial hemorrhages, chills or enlargement of the spleen, and the blood culture was negative. In a bacterial endocarditis producing embolic nephritis, red cells are the first findings to appear. In this case the red cells — just a few — appeared late. I cannot rule out a true glomerulonephritis; we have seen a fair number of cases of subacute glomerulonephritis with a bacterial endocarditis. I should still have to explain the enlarged liver, but I suppose he could have had heart failure in addition to bacterial endocarditis.

In a child of six years the heart disease that I should think of besides rheumatic heart disease is a congenital lesion. If this had been congenital heart disease, in the absence of cyanosis the only congenital anomaly it could have been with a continuous

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murmur is a patent ductus arteriosus, but then the murmur should have been at the base. In an infant it might be hard for the examiner to decide whether the continuous murmur was at the apex or the base, but in a six-year-old child I do not think there should be any difficulty in deciding where the murmur was. To explain the other findings I should have to add bacterial endocarditis, and the same objections hold for a bacterial endocarditis superimposed on a congenital heart as for one on a previously existing rheumatic heart.

In addition to the murmur a conspicuous finding was in the urine. Can I explain the whole picture by renal disease? The urinary findings themselves — the albumin, the casts and the white cells, which increased during the patient's stay in the hospital — would go with a chronic glomerulonephritis. The patient had an elevated blood pressure, a pericarditis demonstrated in the electrocardiogram and convulsions; the last two may have been on a uremic basis. Perhaps the child died in uremia; there were no chemical determinations recorded so that I do not know what the nonprotein nitrogen was. The anemia would also go with a chronic nephritis. Against the diagnosis of a chronic glomerulonephritis is first of all the course, which was much too rapid in a child of six. I do not believe I have ever seen chronic glomerulonephritis in a child of this age; a child usually has an acute nephritis, and red cells appear first in the urine. The urinary findings might fit with a true nephrosis, but the patient had edema of the ankles and legs only and no edema anywhere else, which is certainly against a diagnosis of nephrosis. Usually, also, in a nephrotic patient the blood pressure does not go up. Against uremia are the specific gravities of the urine specimens of 1.020 and 1.025; in a patient who dies of chronic renal disease, the specific gravities are usually in the range of 1.010 continuously. Also, a primary chronic renal disease would not explain the abdominal pain, unless there was a uremic enteritis, which would explain the positive guaiac test on the stool. All in all I do not believe that this is the picture of primary glomerulonephritis.

I believe I have ruled out primary heart disease and primary renal disease, at least to my own satisfaction. In addition to these two organs that were involved in some process, there was involvement of the skin, the liver was enlarged, there was some bleeding from the gastrointestinal tract, the lungs were involved, and the severe anemia suggested involvement of the bone marrow. In other words these findings might fit in with a systemic disease of some sort. I might mention the rare infectious diseases, such as toxoplasmosis or histoplasmosis. When toxoplasmosis affects children, usually infants, it is a cerebral disease; adults have chills, fever and a rash just as this child did. Usually, the outstanding feature in that condition is disease in the lung. It may involve the liver and heart. I doubt, however, if Dr. Means would bring up a case of toxoplasmosis. Histoplasmosis usually produces anemia and fever, but it also produces a leukopenia; this patient had a leukocytosis. In that disease not only the liver but also the spleen and the lymph nodes are involved. In this case there was no evidence of enlargement of the spleen or the lymph nodes.

There is one systemic disease that I believe can account for all the findings and that is polyarteritis nodosa. Patients with polyarteritis nodosa have a fever and quite often have skin lesions perhaps due to arterial changes in the skin. This boy had pain in the muscles of the neck and shoulders, which would fit in with the myositis that accompanies polyarteritis nodosa. The symptoms that brought him into the hospital were abdominal pain and vomiting. Most patients with polyarteritis nodosa have abdominal pain. In a recent paper workers at the Mayo Clinic[1] reported 30 cases of polyarteritis nodosa, of which 21 — that is, 70 per cent — had abdominal pain. They make the statement that the abdominal pain is the most prominent symptom and frequently is in the right upper quadrant. Some patients have even been operated on for an acute abdomen, and the appendix has been removed. Occasionally, changes in those appendixes have been regarded as consistent with polyarteritis nodosa. The pain, usually caused by lesions secondary to the vascular lesions in the organs, may be explained by lesions on the surface of the intestines, or in the capsule of the liver. Very often the arteries or arterioles develop aneurysms, which may rupture and produce hemorrhage and pain in the abdomen. The enlargement of the liver may have been due to infarction within the liver as a result of the arterial change. Often the intestines have small lesions that may cause ulceration of the mucosa. Bleeding from an ulcerated mucosa could account for the positive guaiac test on the stool. Heart involvement is quite common in this disease. Along the pericardium the coronary artery is often involved, and may produce signs of pericarditis in the electrocardiogram and the ischemic changes. How can I explain the continuous murmur? Perhaps the sound was not really a murmur and had nothing to do with the valve, but was due to a rub of the pericardium that was continuous. If I really have to call it a murmur and explain it by disease of the valve rheumatic heart disease, which sometimes does occur with polyarteritis nodosa, may have been present. In fact some years ago Dr. J. B. Hazard[2] had such a case in which he found characteristic Aschoff nodules in the myocardium and polyarteritis nodosa in the other organs. The changes in the lungs could have been due to polyarteritis nodosa, which may produce changes not only in the pulmonary vessels but also in the bronchial vessels.

I believe that the fundamental disease here was polyarteritis nodosa. I cannot find anything against that diagnosis.

Clinical Diagnosis

Rheumatic heart disease, with congestive heart failure.

Dr. Benjamin Castleman's Diagnosis

Polyarteritis nodosa.

Anatomical Diagnoses

Polyarteritis nodosa involving coronary and renal arteries.
Myocardial infarction, recent.
Renal and pulmonary infarcts.
Hydrothorax, bilateral.

Pathological Discussion

Dr. Means: Dr. Castleman did just exactly what I expected he would do.

Dr. Vickery will describe the anatomic diagnoses.

Dr. Austin L. Vickery: I am gratified that it has not fallen on me to drive the knife into Dr. Castleman's back. Dr. Means handed me the major anatomic diagnoses just before this conference, indicating that the patient had polyarteritis nodosa involving primarily the coronary arteries and the renal arteries. The lesions appeared to be in both the acute and the healing stage, with actual thrombosis of the coronary artery and also of the branches of the renal artery. In addition there was a recent myocardial infarct and a mural thrombus in the left ventricle. There were also infarcts in the lungs and the kidneys, which may have accounted for the abdominal pain. A hydrothorax of about 500 cc. on each side was present. Apparently, no lesions were observed in the gastrointestinal tract to account for the guaiac-positive stools.

The only thing I have to add is that I have never seen polyarteritis nodosa in a patient of this age, and since I could not ask Dr. Castleman about that I took a hurried trip to the library and found in Brennemann's book[3] that up to 1937 there had been 230 cases of polyarteritis reported of which 32 were in children; the youngest patient was two and a half months of age. There were 10 cases in which the disease occurred before the age of ten. I could find no evidence that the course was any different in children than in adults.

References

1. Wold, L. E., and Baggenstoss, A. H. Gastrointestinal lesions of periarteritis nodosa. *Proc. Staff Meet., Mayo Clin.* **24**:28-35, 1949.
2. Hazard, J. B. Personal communication.
3. Ward, R. Periarteritis nodosa. In *Brennemann's Practice of Pediatrics*. Vol. 3. Hagerstown: Prior, 1948. Pp. 85-99.

CASE 40122

Presentation of Case

An eighty-year-old widow was admitted to the hospital because of pain along the right costal margin.

About five weeks previously there was apparently sudden onset of pain along the right costal margin and just below the right breast. This pain was described as steady — not throbbing, burning or colicky. Occasionally, it radiated into the right axilla, became progressively more severe and was exaggerated by deep breathing or pressure along the right costal margin. During the five-week period she was nauseated and took little if any food by mouth. For several days immediately before admission she had vomited after every attempt at eating or drinking. There was no history of hematemesis, melena or fever.

Approximately three years before entry intermittent episodes of "indigestion" after meals accompanied by eructation, nausea and occasional vomiting developed. Rarely, such episodes were associated with mild midepigastric pain. She stated that dyspnea on exertion had been present for a long time and that she usually was "too winded" to climb stairs. She preferred to sleep on two pillows, admitted occasional swelling of the right leg and denied the occurrence of chest pain with exertion or paroxysmal nocturnal dyspnea. She had been taking 0.1 gm. of digitalis daily for an unknown period but had discontinued it about a month before admission.

Physical examination revealed a moderately obese woman who was breathing rather rapidly and had slight cyanosis of the lips. She was able to lie flat without difficulty but occasionally cried out with pain, pointing out its location at varying points along the right costal margin. Both the lips and skin were dry. The neck veins were distended when she was raised to 30°, and filled from below but were not pulsatile. The breath sounds were bronchovesicular throughout the lung fields but were decreased in the right axilla. Fine, moist rales were heard over both bases. Vocal fremitus was slightly increased in the

right axilla. The right leaf of the diaphragm was believed to be high. The heart was enlarged, the area of dullness extending 2 cm. beyond the midclavicular line. The rhythm was regular, and the sounds of good quality. A Grade 2, blowing, systolic murmur was heard at the apex. The aortic second sound was greater than the pulmonic. The abdomen was obese and soft. There was considerable tenderness in the right upper quadrant and slight tenderness in the left upper quadrant, both in the absence of rebound tenderness or significant spasm. No organs or masses were palpable. There was no dependent edema.

The temperature was 100°F., the pulse 100, and the respirations 30 to 35. The blood pressure was 124 systolic, 64 diastolic.

Except for the sediment, which contained 5 to 10 white cells per high-power field, the urine was normal. Examination of the blood revealed a hemoglobin of 14.0 gm. per 100 cc. and a white-cell count of 17,600. The sodium was 139 milliequiv., the chloride 105 milliequiv., the potassium 4.0 milliequiv., and the carbon dioxide 28.0 milliequv. per liter; the nonprotein nitrogen was 61 mg., and the fasting blood sugar 141 mg. per 100 cc.

Roentgenograms of the chest demonstrated a small, fairly well defined infiltration in the medial part of the right lower lobe. Two linear shadows were also present in the right lower lobe. The left border of the heart reached the lateral chest wall. There was no fluid in either pleural cavity.

There was little or no change in the patient's status during the first three hospital days. She was treated conservatively with bed rest and received penicillin daily. The temperature curve was irregular, with elevations to 101.0°F., and on the second hospital day the white-cell count was 11,500. A second roentgenogram of the chest showed an increase in size of the area of increased density in the right lower lobe. On the evening of the fourth day there was sudden onset of severe, constricting precordial pain without radiation. With the onset of this pain, dyspnea and cyanosis became even more evident. The blood pressure was 115 systolic, 80 diastolic, and the neck veins were distended and pulsating 8.0 cm. above the clavicles. The pulse was 120, with a gallop rhythm over the precordium. The heart sounds were barely audible because of wheezing respirations. The expiratory phase was prolonged, and moist rales were heard at both bases. Dullness was present at the right base. Some tenderness was still present in the right upper quadrant, and the liver edge was thought to be about three or four fingerbreadths below the right costal margin. An electrocardiogram demonstrated atrial fibrillation at a ventricular rate of 175.

The patient was digitalized and sedated, given oxygen and aminophylline and treated by other supportive measures. On the next day atrial fibrillation had reverted to normal with quinidine. On the sixth hospital day she was still dyspneic and had basal rales and liver enlargement. The cardiac rhythm remained normal. Some tenderness was present in the right calf, but the Homans sign was negative. The circumference of the right calf was 2.5 cm. greater than that of the left. Later the same day there were three episodes of pain in the left side of the chest, each responding promptly to sublingual administration of nitroglycerin. An electrocardiogram showed a sinus tachycardia (rate of 100), a PR interval of 0.19 second and a QRS interval of 0.07 second. Q waves were present in Leads 3 and aVF; the ST segments were sagging in Leads 1, aVL, V_5 and V_6 and depressed in Leads V_3 and V_4, and the T waves were inverted in Leads 1, 2, 3, aVL, aVF, V_5 and V_6. After the last attack the pulse rose to 140. The blood pressure was 110 systolic. The diastolic pressure could not be determined. She suddenly became apneic and cyanotic. An hour after the administration of morphine and the use of multiple tourniquets, she became considerably less cyanotic and tachypneic, and the pulse rate dropped to 120 per minute; however, from that point on she slowly failed. The blood pressure gradually fell, cyanosis became marked, and terminally she lapsed into deep coma. A white-cell count was reported as 21,700. She died later the same day.

Differential Diagnosis

Dr. Henry D. Stebbins*: The onset of pain five weeks before admission was said to have been "apparently sudden." Since it is not really clear whether or not the onset was sudden, I shall have to assume that it was. After admission to the hospital the patient did have an episode of sudden onset of severe pain, so that the two may have been related. The character of the pain — the fact that it was aggravated by deep breathing and pressure on the chest, and was not colicky or burning — seems to place

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its cause above the diaphragm. One thinks of pleural irritation.

The "indigestion" after meals for three years before admission I do not think we have to consider as necessarily a part of the last illness. Indigestion is a vague term and is used by many people to describe symptoms that do not arise from the gastrointestinal tract, the best known of which is probably the "indigestion" that a patient with coronary-artery disease often has when he climbs stairs. This patient's indigestion, however, was not stated to be associated with exertion and was accompanied by eructation, nausea and occasionally vomiting. The mild epigastric pain that she occasionally had with the "indigestion" suggests gall-bladder disease.

How soon after eating did she vomit? Immediately, or an hour or so later, or was that not determined?

DR. BENJAMIN CASTLEMAN: It was not recorded.

DR. STEBBINS: We shall have to assume that she vomited fairly soon after eating. That is somewhat disturbing since I had thought that she probably had a condition above the diaphragm; now we are confronted with the probability of some condition below the diaphragm. For five weeks before admission she had eaten almost nothing, and yet on admission she was "moderately obese." Did she continue to vomit? Was she able to keep anything taken by mouth or was she given intravenous feedings?

DR. J. EHRENKRANTZ: I believe she kept some food down.

DR. STEBBINS: She continued to be somewhat nauseated but did not vomit persistently?

DR. EHRENKRANTZ: Yes.

DR. STEBBINS: It is unfortunate for the discusser that digitalis was discontinued a month before admission; I should have liked to say that she was overdigitalized and therefore was vomiting. As it is, we shall have to assume that the persistent vomiting was connected with her illness.

Did this woman ever have any children?

DR. CASTLEMAN: Yes.

DR. STEBBINS: That is important because I should like to consider the possibility of thrombophlebitis. Moreover, she had occasional swelling of the right leg. Did that go back to the child-bearing era or was it a more recent occurrence?

DR. CASTLEMAN: I do not know.

DR. STEBBINS: That the right calf was 2.5 cm. greater than the left, I think, is of some importance. The patient had a negative Homans sign, however. I think it is safer to neglect a negative Homans sign and assume that she had thrombophlebitis than it would be to neglect a positive one.

It is of considerable interest that with obvious dyspnea, tachypnea and respirations of 30 to 35 per minute she was able to lie flat; that seems to speak against the usual type of congestive heart failure. One thinks of the dyspnea seen in asthma or cor pulmonale after pulmonary emboli, or of the extracardiac dyspnea caused by mediastinal masses or extrinsic pressure on the heart and great vessels.

I should like to know whether the breath sounds were frankly bronchovesicular, or whether this was a misprint. Bronchovesicular breath sounds, which are definitely abnormal, are usually associated with consolidation — possibly patchy consolidation or collapse. That they were heard all over the lung fields, both front and back, suggests that she had extensive parenchymatous lung lesions, which the x-ray films did not show.

DR. CASTLEMAN: That is what is written in the record.

DR. STEBBINS: Did more than one observer record it?

DR. CASTLEMAN: A second observer found a few linear, moist rales.

DR. STEBBINS: I think we can ignore the term "bronchovesicular" because it is not supported by the other findings. The fine moist rales heard over both bases and the increased vocal fremitus in the right axilla suggest a lesion in the right base that had modified the tissues conducting the breath-sounds from the bronchi to the stethoscope.

The blowing systolic murmur at the apex, of Grade 2 intensity, is of a type that can be heard in many elderly patients. Such a murmur could be caused by enlargement of the heart, with dilatation of the mitral ring. Was a blood Hinton test done?

DR. CASTLEMAN: It was negative.

DR. STEBBINS: Because of the accentuated aortic second sound with a normal blood pressure, one must rule out syphilitic aortitis.

To summarize the physical examination, then, there was definite evidence of increased venous pressure, at least in the upper part of the body, some evidence of congestive heart failure with rales at the bases, probable collapse or consolidation in the right lower lung and possibly an enlarged, tender liver.

The laboratory findings were routine for a dehydrated elderly woman although the white-cell

count was perhaps slightly higher than could be accounted for entirely by dehydration. Also, I do not remember seeing a blood sugar as high as 141 mg. per 100 cc. in dehydration.

The electrocardiogram taken on the sixth hospital day, which I have seen, also showed elevation and convexity upwards of the ST segments in Leads 3 and aVF.

May I see the x-ray films?

Dr. Joseph Hanelin: I think one of the striking things about the chest is that the diaphragm is elevated considerably on both sides. There may be some disagreement about the sharply defined infiltration of the medial portion of the right lower lung. I am not certain that we are not looking at normal vascular structures in this area. There are, however, two linear shadows that are present in the lower portion of the lung field that may be due to atelectasis or infarction, but if they are infarction they do not seem to be recent; they may be of some weeks' duration. I do not see any evidence of pleural fluid. The heart does not seem to be remarkably large although it is probably larger than normal; what prominence we see would be mainly of the left ventricle. There is calcification of the aortic arch.

Dr. Stebbins: Are these lung shadows the type that one sees after the healing of old infarcts?

Dr. Hanelin: Yes; they may eventually disappear or may persist indefinitely.

Dr. Stebbins: I should say that there was considerable rotation in this film, with the head of the left clavicle 1 cm. from the spine and the other one overlying the spine by 1 cm., so that the finding of the apex of the heart out to the ribs does not indicate too much cardiac enlargement.

Dr. Hanelin: I think the rotation of the chest and the elevation of the diaphragm could account for it.

Dr. Stebbins: Does this help in deciding about an old pulmonary infarct?

Dr. Hanelin: Not too well; those shadows may be on that basis. They are not abutting upon two pleural surfaces and may be due to discoid atelectasis.

In the next films, made with the patient lying on the back (the other was posteroanteriorly and with the patient erect) the mediastinum seems wider. The difference in rotation may be playing some part in this. However, there is no definite abnormality on the right side, where it was pointed out before, making me strongly believe that we are not dealing with anything in the medial portion of the right lower lobe. There are two basal densities previously described.

Dr. Stebbins: What do you make of this triangular shadow at the right base?

Dr. Hanelin: That may represent a new density in the lung field.

Dr. Stebbins: Would you say that a dissecting aneurysm increasing the caliber of the aortic shadow might produce this shadow? There is calcification here.

Dr. Hanelin: I think that is a consideration, but ordinarily there would also be greater widening of the transverse and proximal descending portions of the aorta.

Dr. Stebbins: Do you have any films of the abdomen and gall-bladder region to show us whether she had radiopaque stones?

Dr. Hanelin: She has some radiopaque densities in the right upper quadrant that could be stones. There is extensive calcification of the abdominal aorta, which is very tortuous, and also of the vessels of the celiac axis. There are two extremely dense calcifications in the right upper part of the abdomen toward the midline that may be stones in the gall bladder, in the pancreas or in some other structure. They are denser than gallstones usually are.

Dr. Stebbins: Are they in the right area for gallstones, or are they too close to the spine?

Dr. Hanelin: They are in the correct area; usually, the gall bladder is situated more laterally, but it is conceivable that it could be in this position.

Dr. Stebbins: The first problem to decide is whether or not to lump everything under one diagnosis or to bring in more than one. At eighty this patient certainly belonged statistically in the age group where multiple diagnoses are more likely. The question of a lesion in the gastrointestinal tract is the one I should like to consider first because that seems to me to be the oldest suggestion in the history. I am willing to accept the opacities as being gallstones, and I shall say that she had old cholecystitis and cholelithiasis, which were probably unrelated to the final illness.

The diagnosis of the condition that caused her death is more difficult. Some physician must have thought she had heart disease because she was given digitalis a long time ago. That does not prove that she did have heart disease, but with the questionable cardiac enlargement and the symptoms that she had

for a good many years, something was probably embarrassing the heart, either intrinsic or extrinsic disease. She had a swollen right leg for a long time; we do not know how long. She had dyspnea without orthopnea and two linear densities in the right lower lobe, which, after looking at the x-ray films, I am willing to accept as old infarcts, so I believe she had thrombophlebitis in the right lower leg and old pulmonary emboli.

To decide whether the final episode that caused her death was related to these previous conditions is more difficult. After having seen the x-ray films showing extensive arteriosclerosis in the aorta, with recent changes in these findings and in the electrocardiogram, I have changed my mind. I had considered coronary occlusion with myocardial infarction and massive pulmonary infarction as the final episode that caused her death. None of the three electrocardiograms look like the picture of acute right-sided heart strain; they resemble more the pattern of posterior myocardial infarction. There is a condition that can produce secondary myocardial infarction, and that is a dissecting aneurysm, although it is unusual in this age group. The patient did have coronary insufficiency with angina, which was relieved by nitroglycerin even in the relatively late stages of the disease, which would be unlike the angina with a full-blown infarction. I think she had extensive arteriosclerosis of the aorta and some of the peripheral vessels, a dissecting aneurysm with dissection around the mouths of the coronary arteries and acute myocardial ischemia with possibly infarction of the posterior wall of the heart.

Clinical Diagnoses

Pulmonary emboli.
Arteriosclerotic coronary-artery disease.
?Myocardial infarction.

Dr. Henry D. Stebbins's Diagnoses

Dissecting aortic aneurysm.
Dissection around mouths of coronary arteries, with myocardial ischemia and ?infarction.
Thrombophlebitis, right lower leg.
Old pulmonary infarcts, right lower lobe.
Arteriosclerosis of aorta.
Cholecystitis.
Cholelithiasis.

Anatomical Diagnoses

Pulmonary embolism, acute, massive.
Coronary-artery disease, severe.
Pulmonary infarcts.
Phlebothrombosis, leg veins, bilateral.

Pathological Discussion

Dr. Castleman: The heart was enlarged, weighing over 460 gm., and showed severe coronary-artery disease. One of the branches of the left circumflex artery, reduced to a pin-point lumen by sclerosis, was completely occluded by a recent thrombus. There was no evidence of recent myocardial infarction, but myocardial fibrosis was present. The cause of death was a massive embolus to the main pulmonary artery, the source being the leg veins; both popliteal veins and their major contributaries were occluded by thrombi. There were smaller emboli in both lungs, and two infarcts were found, one in the right lower and a smaller one in the middle lobe. There were no infarcts in the left lung.

In the abdomen there were a number of conditions, none of which, I believe, had anything to do with the final symptoms. There was diverticulitis of the sigmoid, with some inflammation in the pericolic fat, that might have produced pain in the lower abdomen. We were unable to find any stones in the gall bladder. The radiopacities represented calcified lymph nodes. There was a diverticulum of the esophagus that was somewhat eroded. It is quite possible that some of the pain and vomiting had something to do with that lesion, but certainly most of the pain was caused by the pulmonary infarcts under the breast on the right side.

Dr. Hanelin: How old were they? The last film we have was made three days before she died.

Dr. Castleman: The larger infarct in the right lower lobe was roughly 3.5 cm. in diameter and was older than three days; I think it was about a week old since there was definite organization.

The New England
Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

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MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

HUBBARD 2-5252

CERTAIN elements of the press, often more ready to censure than to praise, gave poor publicity to the local medical profession a number of days ago with the headline that twelve physicians had failed to respond to an emergency call. The unfortunate patient in this instance died on the way to the hospital; fortunately not as a result of the apparent neglect.

The damage having been done, an investigation showed that the emergency medical service established a year and a half ago by Middlesex South, Norfolk and Suffolk District Medical societies to service Boston and Brookline had functioned satisfactorily. A physician was ready to leave for the patient's side within minutes after the call was received, and then the call was canceled. It was at this point, reports state, that resort was had, unmindful of the emergency-call service on which so much time and effort had been expended, to the old haphazard method of ringing doctors' telephones without knowledge of availability. The garden hose was hauled out of the cellar regardless of the organized fire brigade around the corner.

Two lessons are to be learned from this unfortunate experience — a specific local one and a general one of fundamental importance. The first is that within the municipalities of Boston and Brookline, as the result of the co-operative efforts of the three district societies involved, financially supported by the profession and organized through the devoted efforts of Dr. Carl F. Maraldi and his committee, the emergency medical service mentioned above exists. A hundred and fifty physicians are enrolled who make themselves available day and night on a rotating basis. The telephone company has co-operated by instructing its operators to refer all emergency medical calls to the Boston Emergency Physicians' Service, where one or more operators are always at the board to process the calls received and to stick to the job until they are adequately covered. The number is HUbbard 2-5252. Any seeming delay in publicizing this service has been only in the interest of having it smoothly functioning before full knowledge of it was released. Such a service is, of course, not peculiar to Boston. Many other cities and towns not in Massachusetts but over the country in general are benefiting from similar service agencies.

The second lesson to be learned from the unhappy episode mentioned above is that of common-sense personal preparedness on the part of the public. Rarely is the family that has enlisted the services of a regular, responsible family physician caught in the predicament of knowing not where to turn when the sudden emergency arises. For the responsible practitioner is able nearly always to care for his own or to arrange for their care when he cannot personally attend them.

"TO THE EDITOR —"

THE art of letter writing, as an amenity of modern man's hurried progress through life, has become, to a considerable extent, one of the lost ones. Famous persons of the past, much more than those of the present, were characterized by their personal correspondence and sometimes best interpreted by the intimate revelations of their private journals; but how many are there today who keep a diary with the

detail and fidelity of a Pepys, or regularly post a log like that of Admiral Evans, which can be drawn on later in preparing the memoirs of an active career?

This change in intellectual habit is due not necessarily so much to an increase in the number of one's interests — if one is willing to put a limit on them — as to their time-consuming quality. Even more important are the forms of entertainment, so-called, and the insistent agencies of communication that intrude upon one's solitude, and the extraordinary mobility of man that allows him to remain in the same place for such short periods of time. These pressures leave the average person of normally limited energy little opportunity to record in correspondence or in diary the results of his reflections, if, indeed, he has not entirely lost touch with that form of communion.

Even in medicine, the most literarily productive of the professions, —with the possible exception of that of letters, — the pen of the producer is not often employed with facility or for other purposes than the relation of purely factual material. To a nonmedical editor has been attributed the profundity that "except for medical literature, all good writing has a conversational quality."

Whether this statement was intended as an adverse criticism or as the simple recording of a fundamental and inescapable fact was not mentioned.

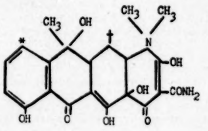
Regardless of the reasons for the decline in its exercise, it has long been accepted that one of the privileges of living in a free and literate society is that of writing to the editor for purposes of publication, if the message is reasonably politic, apparently pertinent and moderately legible to both editor and printer. Under such circumstances a correspondence column can become, if not a thing of beauty, at least a joy forever.

At the risk of an unwarranted accusation of Anglophilia it must be admitted that the British physician favors his journals with an ampler, more variegated and spicier correspondence than do his apparently less articulate colleagues in this country. Considering the amount of paper work to which the British doctor must now square away, this seems like an amazing performance; or perhaps, having his pen in hand, he goes on writing through sheer inertia. Some of the American journals (present company not excepted) might be a little livelier were their readers to express themselves more freely through the informal vehicle of correspondence.

TETRACYCLINE, A NEW ANTIBIOTIC

Ever since oxytetracycline became available it has been strongly suspected of being closely related to the earlier antibiotic, chlortetracycline. This surmise was based on the almost identical antimicrobial spectrum of the two agents in vitro, the similar clinical effects obtained from their use and the almost complete cross resistance between them in organisms repeatedly exposed to increasing concentrations of one or the other. The important differences that have been constant have been related to some chemical and physical properties, particularly stability under various conditions. Quantitative dissimilarities in activity against individual species or strains have also been noted in vitro. Similar diversity in results in individual cases or groups of cases and in the incidence and severity of untoward effects has been reported by various workers. Experience has varied widely in these respects, however, and the results reported are often conflicting.

The basis for the similarity of the two antibiotics became clear with the demonstration of their almost identical chemical structures, as previously pointed out in these columns.[1] The structure common to both of them is as follows:



This has been given the generic name tetracycline. The generic name chlortetracycline is based on the fact that this drug contains a C_1 atom at the position marked "*", and that of oxytetracycline on the fact that it has an OH group at the position marked "†". The original names of these antibiotics, Aureomycin and Terramycin, were adopted as trademarks by the Lederle Laboratories and Charles Pfizer and Company, Incorporated, respectively.

Tetracycline itself has now been produced by the research workers of both these manufacturers and by an identical process, which involved the catalytic hydrogenation of chlortetracycline, palladium being the catalyst that resulted in removal of the organic chlorine. A similar and probably identical substance has been produced directly from a new streptomyces species isolated from a sample of soil obtained in Texas.

The physical, chemical and antimicrobial properties of tetracycline were described in a series of papers presented at the Antbiotic Symposium in Washington on October 28, 1953, and now published as *Antibiotics Annual, 1953-1954.* The results of preliminary clinical trials were also presented at that symposium. The clinical and laboratory experiences with this agent at the Boston City Hospital were recently described by Finland and his co-workers.[2]

All these studies have indicated the close similarity of all three of these tetracycline analogues. The major advantages of tetracycline over its two predecessors appear to be its greater stability, especially in solution; its better absorption and penetration, which result in somewhat higher and more prolonged blood levels from oral administration and also relatively higher concentrations in cerebrospinal fluid; and, probably most important practically, the lower incidence of severe and troublesome gastrointestinal complications, particularly diarrhea, that has resulted from its use clinically.

Tetracycline first became available commercially under the Lederle trademark of Achromycin and has more recently been made available under the trademark Tetracyn by J. B. Roerig and Company, Division, Charles Pfizer and Company, Incorporated.

References

1. Editorial. New generic names for antibiotics. *New Eng. J. Med.* 249:503, 1953.
2. Finland, M., et al. Clinical and laboratory observations of new antibiotic, tetracycline. *J. A. M. A.* 154:561-568, 1954.

MEDICAL EDUCATION: ITS COST TO THE STUDENT

THE *Journal of Medical Education* has presented in its issue of February, 1954, the results of a study conducted by the Association of American Medical Colleges on the cost to the student of medical-school training in the United States today. The average over-all figure, based on questionnaires sent to students of twenty-six medical schools, is $9200. This sum represents the cost of the four-year school training only; the premedical period is not included, nor are any expenses associated with the intern and resident years.

Further information was obtained on this subject, so important to the future of medical practice. A third of the students who responded to the questionnaire expected to have accumulated debts by the time of graduation amounting to an average of $3500. Most of the single students derive their support from their parents; most of the married ones from their wives. When they need to borrow money they apparently avoid their parents, whose annual income averages $7000, in favor of other available sources.

The pursuit of medicine apparently remains — on the average — a solid, substantial, middle-class, middle-of-the-road-affair. This is probably as it should be, if enough provision can be made for the poor boy or girl with the desire and the capacity for entering such an exacting profession.

Dr. Spear, of Melonville, Florida, has raised 20,000 lemons from 250 trees. He is the largest lemon-grower in the country.

Boston M. & S. J., *March 29, 1854*

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S REPORT COVERING REFUND DISTRIBUTION

The Committee on Finance has voted to distribute the sum of $4000 to the district societies for the year 1954. The total number of payments received by March 1, in time to count for the refund, was 4505, making the refund for each paid member $0.8879.

The following table gives the number of payments as of March 1 for each district, and the numerical change from last year's figures. This year Norfolk District deserves special commendation.

The actual amount of the refund to each district is shown as of March 11, 1954.

District	No. Reported Paid	Refund
Barnstable	46 (up 12)	$ 40.84
Berkshire	122 (down 11)	108.32
Bristol North	69 (up 10)	61.27
Bristol South	206 (up 5)	182.91
Essex North	168 (no change)	149.17
Essex South	250 (up 6)	221.98
Franklin	41 (up 3)	36.40
Hampden	324 (up 2)	287.68
Hampshire	57 (up 3)	50.61
Middlesex East	131 (up 8)	116.32
Middlesex North	108 (up 8)	95.89
Middlesex South	796 (down 1)	706.77
Middlesex West	98 (no change)	87.01
Norfolk	812 (up 34)	720.98
Norfolk South	158 (up 4)	140.29
Plymouth	133 (up 1)	118.09
Suffolk	576 (down 31)	511.43
Worcester	317 (up 3)	281.46
Worcester North	93 (up 6)	82.58
	4505 (up 62)	$4000.00

ELIOT HUBBARD, JR., M.D., *Treasurer*

DEATHS

HARTWELL — Ivan G. Hartwell, M.D., of Sandwich, died on March 9. He was in his forty-seventh year.

He is survived by his widow.

KING — Richard B. King, M.D., of West Falmouth and Boston, died on March 9. He was in his fifty-fifth year.

Dr. King received his degree from Harvard Medical School in 1925. He was a member of the staff of the Massachusetts Memorial Hospitals.

He is survived by his widow, a daughter, a son and a brother.

LANE — C. Guy Lane, M.D., of Boston, died on March 12. He was in his seventy-second year.

Dr. Lane received his degree from Harvard Medical School in 1908. He was clinical professor of dermatology, emeritus, Harvard Medical School, and formerly chief of dermatology, Massachusetts General Hospital, president of the American Dermatological Association, New England Dermatological Society, American Board of Dermatology and Syphilology and American Academy of Dermatology and Syphilology. He was a fellow of the American Medical Association and a member of the British Association of Dermatology, French Society of Dermatology, New England Roentgen Ray Society, and the editorial board of the *New England Journal of Medicine*.

He is survived by his widow and a son.

MORRIS — Ernest M. Morris, M.D., of Newton, died on March 6. He was in his sixty-seventh year.

Dr. Morris received his degree from McGill University Faculty of Medicine in 1914. He was a member of the faculties of Boston University School of Medicine and Harvard School of Public Health, and director of public health in Newton and formerly in Fall River.

He is survived by his widow and a brother.

SYLVESTER — Philip Haskell Sylvester, M.D., of Damariscotta, Maine (formerly of Boston) died on March 12. He was in his seventy-fourth year.

Dr. Sylvester received his degree from Harvard Medical School in 1906. He was visiting and consulting physician, Miles Memorial Hospital, Damariscotta, and chief of pediatrics, Bath Memorial Hospital, Bath, Maine. He was a fellow of the American Academy of Pediatrics and the American Medical Association, and a member of the New England Pediatric Society.

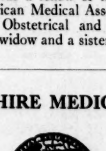
He is survived by his widow.

WALTON — William J. Walton, M.D., of Dorchester, died on March 10. He was in his eighty-first year.

Dr. Walton received his degree from Harvard Medical School in 1897. He was formerly senior obstetrician, St. Mary's Lying-in Hospital, Dorchester, a councilor of the Massachusetts Medical Society, and president of the Norfolk District and Dorchester Medical societies. He was a fellow of the American College of Surgeons and the American Medical Association, and a member of the New England Obstetrical and Gynecological Society.

He is survived by his widow and a sister.

NEW HAMPSHIRE MEDICAL SOCIETY



APPOINTMENT OF DR. BUTTERFIELD

Dr. Warren H. Butterfield, of 17 North State Street, Concord, New Hampshire, has been appointed secretary-treasurer of the Society, effective January 1, after the resignation of Dr. Deering G. Smith.

BOSTON MEDICAL LIBRARY

IN AND ABOUT HOLMES HALL

As the capital fund drive for the Boston Medical Library continues to progress, a natural corollary is a growing interest in the institution itself.

Recently, a young veteran of Korea, who had been home less than a week, came to browse around and become generally acquainted with the Library. He considered this a fitting preliminary to entering Harvard Medical School.

Requests for information and material come from all parts of the world. If an accurate answer exists, the Library will usually furnish it. The range may vary from the effect of acetylcholine and epinephrine on the clam heart to the story of patent medicine outdoor advertising before the 20th century. Thus quietly and unobtrusively the Library makes its contribution to medical science.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY, 1954

RÉSUMÉ

DISEASE	FEBRUARY 1954	FEBRUARY 1953	SEVEN-YEAR MEDIAN
Chancroid	3	3	3
Chicken pox	1449	4227	2070
Diphtheria	1	0	13
Dog bite	714	523	583
Dysentery, bacillary	96	24	6
Encephalitis, infectious	4	1	2
German measles	132	301	143
Gonorrhea	197	183	186
Granuloma inguinale	0	0	0
Hepatitis, infectious	152	83	101†
Lymphogranuloma venereum	0	2	2
Malaria	0	0	0
Measles	171	217	2021
Meningitis, meningococcal	9	6	6
Meningitis, Pfeiffer bacillus	4	2	4
Meningitis, pneumococcal	1	2	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	1	0	0
Meningitis, undetermined	8	5	5
Mumps	2191	1024	1301
Poliomyelitis	6	0	0
Salmonellosis	33	10	4
Scarlet fever	727*	628	627
Syphilis	250	79	168
Trichinosis	3	1	1
Tuberculosis, pulmonary	213	183	183
Tuberculosis, other forms	14	6	10
Typhoid fever	2	1	1
Undulant fever	1	2	2
Whooping cough	238	109	269

*Includes streptococcal sore throat.

†Five-year median.

COMMENT

Diseases below the seven-year median included chicken pox, diphtheria, German measles, measles and whooping cough.

The 1449 cases of chicken pox reported make this the lowest figure for the month of February since 1946.

The 1 reported case of diphtheria is in marked contrast to February of former years, — 1924, for example, when 829 cases were reported.

The 171 cases of measles reported represented the lowest figure by a considerable margin for the month of February in

the history of this state. This continues a trend of more than a year.

Diseases above the seven-year median were bacillary dysentery, infectious hepatitis, mumps, poliomyelitis, salmonellosis and scarlet fever.

The enteric diseases, although showing monthly fluctuations of late, have generally remained at a high level.

The 2191 cases of mumps reported make this the highest figure for the month of February since 1936.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Diphtheria: Braintree, 1.

Dysentery, amebic: Newton, 1; Wrentham, 4; total, 5.

Dysentery, bacillary: Amherst, 1; Ashland, 3; Belchertown, 1; Boston, 15; Danvers, 1; Fitchburg, 1; Haverhill, 1; Malden, 4; Revere, 2; Southboro, 1; Tewksbury, 4; Worcester, 18; Wrentham, 44; total, 96.

Encephalitis, infectious: Lynn, 1; Malden, 1; Natick, 1; Weymouth, 1; total, 4.

Hepatitis, infectious: Belchertown, 3; Belmont, 2; Boston, 31; Brookline, 1; Brockton, 9; Cambridge, 12; Chelsea, 8; Chicopee, 1; Clinton, 1; Everett, 2; Fall River, 2; Greenfield, 6; Haverhill, 1; Lancaster, 1; Lawrence, 1; Leicester, 2; Lowell, 1; Lynn, 13; Malden, 1; Mansfield, 1; Milton, 1; Natick, 1; Newton, 4; Northampton, 2; Norton, 1; Oxford, 1; Peabody, 1; Pittsfield, 1; Plymouth, 5; Quincy, 5; Revere, 2; Salem, 1; Sharon, 1; Springfield, 5; Taunton, 4; Warren, 2; Webster, 2; Wellesley, 1; Westport, 1; Wilbraham, 2; Williamstown, 3; Worcester, 6; Wrentham, 1; total, 152.

Meningitis, meningococcal: Ayer, 1; Boston, 5; New Bedford, 1; Pittsfield, 1; Worcester, 1; total, 9.

Meningitis, pneumococcal: Springfield, 1.

Meningitis, Pfeiffer bacillus: Boston, 1; Georgetown, 1; Holliston, 1; Worcester, 1; total, 4.

Meningitis, streptococcal: Weymouth, 1.

Meningitis, mumps: Cambridge, 1; Newton, 1; Norwood, 2; Quincy, 1; total, 5.

Meningitis, undetermined: Canton, 1; Chesterfield, 1; Fall River, 1; Falmouth, 1; Peabody, 1; Taunton, 2; Watertown, 1; total, 8.

Poliomyelitis: Auburn, 1; Danvers, 1; Middleboro, 1; Northampton, 1; Pittsfield, 1; Taunton, 1; total, 6.

Salmonellosis: Attleboro, 1; Auburn, 1; Barre, 1; Belmont, 2; Boston, 4; Cambridge, 4; Clinton, 1; Fall River, 1; Lancaster, 1; Malden, 4; Needham, 1; Newton, 1; Salem, 1; Somerville, 1; Watertown, 5; Weymouth, 1; Worcester, 3; total, 33.

Trichinosis: Boston, 3.

Typhoid fever: Boston, 1; Braintree, 1; total, 2.

Undulant fever: Wilmington, 1.

CORRESPONDENCE

ACT RELATIVE TO DEATH CERTIFICATES

To the Editor: On February 23 the Governor approved an act requiring physicians to print or type causes of death on certificates of death. I have received a copy of this law from Mr. Edward J. Cronin, Secretary of the Commonwealth, and that this recently enacted legislation may come to the attention of the members of the Massachusetts Medical Society, a copy is included below.

JOHN H. CAULEY, M.D., M.P.H.
Health Commissioner

Boston

Chapter 137

The Commonwealth of Massachusetts

In the Year One Thousand Nine Hundred and Fifty-Four an Act REQUIRING CAUSES OF DEATH TO BE PRINTED OR TYPED ON CERTIFICATES OF DEATH.

Be it enacted by the Senate and House of Representatives in General Court assembled, and by the authority of the same, as follows: Section 9 of Chapter 46 of the General Laws, as most recently amended by Chapter 113 of the acts of 1945, is hereby further amended by inserting after the first sentence the following sentence:— The cause, or causes, of death shall be printed or typed on all certificates required to be furnished under this section.

House of Representatives, Feb. 11, 1954.
Passed to be enacted, Charles Gibbons, Speaker.

In Senate, Feb. 16, 1954.
Passed to be enacted, Richard I. Furbish, President.

February 23, 1954
Approved,

CHRISTIAN A. HERTER
Governor

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Manual of Medical Emergencies. By Stuart C. Cullen, M.D., professor of surgery and chairman, Division of Anesthesiology, State University of Iowa College of Medicine; and E. G. Gross, M.D., professor of pharmacology and head, Department of Pharmacology, State University of Iowa College of Medicine. Second edition. 12°, cloth, 278 pp., with 34 illustrations. Chicago, Illinois: Year Book Publishers, Incorporated, 1953. $4.50.

This small manual was first published in 1949 and reprinted twice before the printing of this second, revised edition. Material has been added to the chapters on airway and artificial respiration, circulatory emergencies and acute poisoning. There is a good index, and the small book is well printed.

Shock and Circulatory Homeostasis: Transactions of the Second Conference, October 19, 20, and 21, 1952, Princeton, New Jersey. Edited by Harold D. Green, M.D., professor of physiology and pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina. 8°, cloth, 275 pp., with 57 illustrations. New York: Josiah Macy, Jr., Foundation, 1953. $3.75.

This is a relatively new conference in the series sponsored by the Josiah Macy, Jr., Foundation and an important one on shock. Two subjects were extensively discussed by the members of the conference: the metabolic aspects of hemorrhagic and traumatic shock, and the distribution and possible physiologic functions of epinephrine and nor-epinephrine. Lists of references are appended to the respective sections.

Renal Function: Transactions of the Fourth Conference, October 22, 23, and 24, 1952, New York, New York. Edited by Stanley E. Bradley, M.D., associate professor of medicine, Columbia University College of Physicians and Surgeons. 8°, cloth, 189 pp., with 47 illustrations and 29 tables. New York: Josiah Macy, Jr., Foundation, 1953. $3.50.

The contents of this fourth volume of a reference series include ion exchanges between extracellular and intracellular fluids, cation exchanges in the tubular epithelium of the kidneys, ion transport across living membranes and water and ion movements across intestinal and renal epithelium.

The Ballistocardiogram: A dynamic record of the heart beat. By John R. Braunstein, M.D., Ph.D., associate professor of biophysics and assistant professor of medicine, University of Cincinnati College of Medicine. 8°, cloth, 84 pp., with 41 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $3.00. (Publication No. 143, *American Lecture Series.*)

In this monograph the author discusses the various aspects in the light of present-day knowledge. The literature is evaluated; there is a bibliography of seven and a half pages and a good index. The small book should be in all collections on cardiology.

Living with a Disability. By Howard A. Rusk, M.D.; and Eugene J. Taylor. With the collaboration of Muriel Zimmerman, O.T.R.; and Julia Judson, M.S., Institute of Physical Medicine and Rehabilitation, New York University-Bellevue

Medical Center. 8°, cloth, 207 pp., with 282 illustrations. Garden City, New York: The Blakiston Company, 1953. $3.50.

The material in this textbook edition is based on two surveys made under the sponsorship of the National Foundation for Infantile Paralysis. All known devices intended for aiding the physically handicapped were tested, and the information obtained is now made generally available to all interested persons. The text is written in an easy popular style and profusely illustrated. It might be said that there are more pictures than reading matter. There is a good index, and the publishing is excellent.

European Seminar and Lecture Course on Alcoholism: Sponsored by the Royal Danish Government in cooperation with the World Health Organization and the United States, Copenhagen, 22 October — 3 November 1951. 8°, paper, 121 pp., with 8 illustrations and 3 tables. Geneva, Switzerland: Printed and distributed by the Regional Office for Europe of the World Health Organization, 1952. Not for sale.

The proceedings of this seminar present current knowledge of alcoholism from the medical point of view. The papers are divided into five parts: physiologic aspects of the use of alcoholic beverages; the etiology of alcoholism; the clinical picture and special features of the disease; treatments for the arrest of the alcoholic drinking behavior; and public care and the prevention of alcoholism. The document is not for sale. A limited number of copies are available for libraries and health institutions and may be obtained from the European regional office of the W.H.O., Palais des Nations, Geneva, Switzerland.

The Obstetrical Forceps. By L. V. Dill, M.D., head, obstetrics and gynecology, Yater Clinic, assistant professor, obstetrics and gynecology, Georgetown University School of Medicine, consultant, obstetrics and gynecology, Army Medical School and Walter Reed General Hospital, and staff member, obstetrics and gynecology, Providence Hospital, Washington, D. C. 8°, cloth, 156 pp., with 86 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $5.25. (Publication No. 150, *American Lecture Series.*)

This monograph discusses the use and application of the obstetric forceps in the various types of delivery. There are special chapters on the Tarnier, Kjelland, Barton and Piper forceps, and the choice of forceps. The text proper is preceded by two chapters on the history and development of the forceps in its present form. There is a short bibliography and a good index; the text is well illustrated, and the publishing is excellent. The small book should be in all collections on obstetrics. The small monograph of today is a valuable contribution to medical literature.

Hyperparathyroidism. By B. Marden Black, M.D., associate professor of surgery, Mayo Foundation for Medical Education and Research Graduate School, University of Minnesota, and Division of Surgery, Mayo Clinic, Rochester, Minnesota. 8°, cloth, 119 pp., with 19 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $3.75. (Publication No. 173, *American Lecture Series.*)

A preliminary chapter is devoted to a short history of the disease from the description by Recklinghausen in 1891 to the present time. The author states that the condition "is a relatively common, potentially fatal disease, which, if treated before irreversible renal damage has been produced, is curable in the great majority of cases." He discusses the pathologic histology, clinical aspects, diagnosis and differential diagnosis and treatment, including surgery. A bibliography of 112 references is appended to the text, and there is a good index.

The Surgery of Infancy and Childhood: Its principles and techniques. By Robert E. Gross, M.D., D.Sc., William E. Ladd Professor of Children's Surgery, Harvard Medical School, and chief, Surgical Service, Children's Hospital, Boston. 8°, cloth, 1000 pp., with 1488 illustrations. Drawings by Etta Piotti. Philadelphia: W. B. Saunders Company, 1953. $16.00.

Dr. Gross bases his work on twenty years' experience in the field of surgery of children. He has had exceptional opportunities at the Boston Children's Hospital and Harvard Medical School, and his book represents a practical experience in pediatric surgery on thousands of babies and children. The preliminary chapters are general, and are followed by discussions on every type of surgery, including chapters on treatment of patent ductus arteriosus and the tetralogy of Fallot. Lists of references are appended to the chapters; there is a good index, and the publishing is excellent. This outstanding book is recommended for all medical libraries and to pediatricians and surgeons.

Rorschach Interpretation: Advanced technique. By Leslie Phillips, Ph.D., director of psychologic research, Worcester State Hospital, and associate professor of psychology, Clark University, Worcester; and Joseph G. Smith, Ph.D., research assistant, Commission on Human Resources and Advanced Training, Washington, D. C. 8°, cloth, 385 pp. New York: Grune and Stratton, 1953. $8.75.

This book is primarily intended for practical clinical reference and presents relations between Rorschach performance and other behavior. The work is based on a large number of cases, over 1000, checked against 200 normal children and 250 normal adults. The book is well published.

The Living Brain. By W. Grey Walter, M.A., Sc.D. (Cantab.). 8°, cloth, 311 pp., with 23 illustrations. New York: W. W. Norton and Company, Incorporated, 1953. $3.95.

Dr. Walter begins this semi-popular book on the mechanics of the brain as revealed by the electroencephalogram with a history of the evolution of the brain and then describes the invention of the electroencephalograph and its clinical use for the diagnosis of brain conditions. Next he discusses what light the new electronic processes can throw on memory, vision, fatigue, sleep, hypnotism, genius and similar problems. There is an index, and the book is well published.

Integration linearer kutaner Schmerzreize: Eine neurologische und klinischneurophysiologische Studie. By Alf Breig. 8°, paper, 65 pp., with 39 illustrations. Stuttgart: Georg Thieme, 1953. DM 7.20. (Distributed by Grune and Stratton, New York.)

This monograph presents the results of the study and experiments on the physiology of pain carried out at the neurological section of the Serafim Hospital in Stockholm. The text is in two parts: neurologic and cliniconeurologic. There is a bibliography and a survey of the literature. The text is well illustrated.

Pulmonary Tuberculosis: A handbook for students and practitioners. By R. Y. Keers, M.D., F.R.C.P. (Edin.), F.R.F.P.S. (Glas.), F.R.S.E., medical director, Red Cross Sanatoria of Scotland; and B. G. Rigden, M.R.C.S. (Eng.), L.R.C.P. (Lond.), physician, Lewes Chest Clinic and director, East Sussex Mass Radiography Unit. With a new foreword by F.H. Young, O.B.E., M.D. (Camb.), F.R.C.P. (Lond.), D.P.H., physician, Brompton Hospital for Consumption and Diseases of the Chest, consulting physician, Charing Cross Hospital and Red Cross Sanatoria of Scotland, and medical officer in charge of the Tuberculosis Dispensary, St. Bartholomew's Hospital. Third edition. 12°, cloth, 324 pp., with 150 illustrations. Edinburgh: E. and S. Livingstone, Limited, 1953. (Distributed by Williams and Wilkins, Baltimore, Maryland.) $5.50.

The authors have thoroughly revised this new edition of their handbook. The chapter on treatment has been completely rewritten to include new material on chemotherapy, collapse therapy and thoracic surgery. A section on the minimal lesion has been added. The chapters on bacteriology, examination and complications have been extensively revised.

Einführung in die innere Medizin. By Dr. Hans Julius Wolf, special professor of internal medicine, Universität Göttingen, supervisory physician-in-chief, Städtischen Krankenhauses in Bielefeld and physician-in-chief, Internal Division. Fifth enlarged edition. 8°, cloth, 714 pp., with 90 illustrations. Stuttgart: Georg Thieme, 1953. DM 35—. (Distributed by Grune and Stratton, New York.)

This new edition of a standard textbook on clinical medicine has been revised and enlarged. It is comprehensive in scope, covering the whole field of medicine. There is a good index, and the publishing is excellent.

Dermatologic Formulary from the New York Skin and Cancer Unit, Service of Dermatology. (Dr. Marion B. Sulzberger, Director.) Frances Pascher, M.D., editor. 12°, cloth, 150 pp. Paul B. Hoeber, Incorporated, 1953. $3.00.

This formulary is the product of actual composite experience gained since 1882 by leading dermatologists in what is probably the largest paid outpatient service of dermatology in the world.

Leistungssteigerung: Leistung. Übermüdung Gesunderhaltung. By Prof. Dr. Max Hochrein, physician-in-chief, Medizinischen Klinik, Ludwigshafen am Rhein, and Doz. Dr. Irene Hochrein-Schleicher, Ludwigshafen am Rhein. Third revised edition. 8°, cloth, 283 pp., with 53 illustrations and 20 tables. Stuttgart: Georg Thieme, 1953. DM 27.— (Distributed by Grune and Stratton, New York.)

This important monograph, which was previously published in 1942 and 1944, is based on the first German university institute for industrial medicine. This third edition has been revised and amplified. Material on the pathogenesis of overfatigue has been added. The chapters deal with health in general, performance, overfatigue and the maintenance of health, achievement and efficiency. The general theme is the enhancement of work performance. There is a bibliography of 21 pages and a good index. The book should prove useful to all persons interested in industrial and preventive medicine.

Bakteriologische Nährböden: Ausgewählte Nährbodenrezepturen für das medizinisch-bakteriologische Laboratorium. By Dr. Lothar Hallmann. 8°, cloth, 252 pp., with 52 illustrations. Stuttgart: Georg Thieme, 1953. DM 19.80. (Distributed by Grune and Stratton, New York.)

This manual presents formulas of culture mediums for the medical and bacteriologic laboratory. The text is divided into two main sections, the first of which considers mediums in general and presents a list of reagents, indicators and solutions, and the second of which describes the various types of mediums and culture mediums for different organisms. The manual should prove useful in the laboratory.

Acta Radiologica, 1953. Stockholm, Sweden. 8°, paper. Supplementum 99. *Investigations on Backflow in Retrograde Pyelography: A roentgenological and clinical study.* By Rolf Köhler. 92 pp., with 39 plates. Sw. Kr. 20:-

Supplementum 100. *Post-Irradiative Prophylactic Extraperitoneal Lymphadenectomy Carcinoma of the Uterine Cervix.* By Gunnar Gorton. 203 pp., with 15 illustrations and 37 tables. Sw. Kr. 20:-

Supplementum 101. *The Value of Tomography in Examination of the Intrapulmonary Bronchi.* By Herman Lodin. 109 pp., with 47 illustrations. Sw. Kr. 20:-

Supplementum 102. *Microangiography.* By Sven Bellman. 104 pp., with 56 illustrations. Sw. Kr. 20:-

Supplementum 103. *Principles of Vertebral Tomography.* By Ingemar Bokström. 126 pp., with 67 illustrations. Sw. Kr. 20:-

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Surgical Technique and Principles of Operative Surgery. By A. V. Partipilo, M.D., associate clinical professor of surgery, Stritch School of Medicine of Loyola University, senior attending surgeon, Columbus Hospital, senior attending surgeon, St. Mary's Hospital, attending surgeon and chief, Surgical Staff, Mother Cabrini Hospital, consulting surgeon, Chicago State Hospital, and consulting surgeon, Cuneo Memorial Hospital, Chicago. With a foreword by Alton Ochsner, M.D., William Henderson Professor of Surgery and Director, Department of Surgery, Tulane University of Louisiana School of Medicine. Fifth edition. 4°, cloth, 704 pp., with 998 illustrations. Original illustrations by W. C. Shepard and Hooker Goodwin. Philadelphia: Lea and Febiger, 1953. $15.00.

The author, in this new edition of his textbook, has had the assistance of 10 contributors. The text has been revised and brought up to date. Some chapters have been rewritten, and two new ones included on fluid therapy, on surgery and on radiotherapy in carcinoma of the breast. Lists of references have been appended to some of the chapters. There is a good index, and the book is well illustrated.

Die Beurteilung der Zurechnungsfähigkeit: Ein Vortrag. By Kurt Schneider, professor, Universität Heidelburg. Second edition. 8°, paper, 36 pp. Stuttgart: Georg Thieme, 1953. DM 2.70. (Distributed by Grune and Stratton, New York.)

The author discusses the problem of responsibility, especially for jurists and psychiatrists.

Die Bewegungsbestrahlung. By Dr. F. Wachsmann, lecturer in medical physics, and Dr. G. Barth, lecturer in radiotherapy and physical therapy, Universität Erlangen. 8°, cloth, 192 pp., with 124 illustrations. Stuttgart: Georg Thieme, 1953. DM 36.— (Distributed by Grune and Stratton, New York.)

This comprehensive monograph discusses "movement" radiation therapy in all its aspects, including a survey of the pertinent literature. The material is divided into the following five main sections: general principles, rotation, oscillation, convergence and ultra "hard" radiation. There is a bibliography of 196 items. The book should be in all collections on radiology.

Die Kreuzschmerzen der Frau: Ihre Deutung und Behandlung. Gynäkologische Orthopadie. By Prof. Dr. Heinrich Martius, director, Universitäts-Frauenklinik, Göttingen. Fourth revised edition. 8°, cloth, 166 pp., with 73 illustrations, after black-and-white drawings by Käthe Droysen. Stuttgart: Georg Thieme, 1953. DM 19.50. (Distributed by Grune and Stratton, New York.)

This fourth edition of a monograph on backache in women first published in 1939 has been revised to include advances since the printing of the previous edition in 1946. There is a bibliography of 19 pages and a survey of the literature.

Sympathikus-Chirurgie. By Prof. Dr. Paul Sunder-Plassman, director, Chirurgischen Klinik und Poliklinik der Universität Münster (Westf.). 4°, cloth, 162 pp., with 146 illustrations. Stuttgart: Georg Thieme, 1953. DM 54—. (Distributed by Grune and Stratton, New York.)

This semiatlas discusses the surgery of the sympathetic nervous system. The first chapters, which deal with the periphery, paths and centers, are followed by chapters on indications, technic and collateral applications. The book is an exceptional example of excellent publishing. It is recommended for all collections on surgery and diseases of the nervous system.

Zur Genese des Diabetes mellitus und des Bronchialasthmas. Edited by Prof. Dr. M. Bauer, on commission from the Bundesministeriums für Arbeit. With an introduction by Dr. Cl. Dierkes, chief officer, Medical Board, and with an appendix. 8°, paper, 113 pp., with 5 illustrations. Stuttgart: Georg Thieme, 1953. DM 9.60. *Arbeit und Gesundheit: Sozialmedizinische Schriftenreihe aus dem Gebiete des Bundesministeriums für Arbeit. Neue folge Heft 49.* (Distributed by Grune and Stratton, New York.)

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in Sherman Auditorium, Beth Israel Hospital, on Tuesday, April 13, at 8 p.m. The program will be presented by the Department of Medicine, Beth Israel Hospital, with Dr. Herrman L. Blumgart presiding.

PROGRAM

Studies on Amino Acid Metabolism in Infectious Hepatitis. David Yi-Yung Hsia and Sydney S. Gellis.

SPCA-Induced Thrombosis: Its pathogenesis and the effect of anticoagulants. Stanford Wessler.

Elevated SPCA (Convertin) Complex in Pregnancy: Its possible role in pathogenesis of thromboembolism. Benjamin Alexander, Lillian Meyers, Robert Goldstein, Victor Gurewich and Lester Grinspoon.

Control of Cardiac Arrhythmias with Externally Applied Electric Current. Paul M. Zoll, Leona R. Norman and Arthur J. Linenthal.

TUFTS POSTGRADUATE COURSES

A refresher course in clinical medicine for general practitioners will be given at the Beth Israel Hospital, Boston, Massachusetts. The course will be for a month and may be taken in July, August or September. Fellowships, including an honorarium of $250, have been made available under the provisions of the Dr. Nathan Sidel Teaching Fund. Further information may be obtained from the Tufts Postgraduate Courses, Beth Israel Hospital, Boston 15, Massachusetts.

AMERICAN CANCER SOCIETY FELLOWSHIP

The Vincent Memorial Hospital of the Massachusetts General Hospital (Gynecologic Service) announces a fellowship in cancer research under the auspices of the American Cancer Society for one year beginning July 1. Further information may be obtained from Dr. Joe V. Meigs, Vincent Memorial Hospital, Fruit Street, Boston 14, Massachusetts.

MASSACHUSETTS ASSOCIATION OF MEDICAL TECHNOLOGISTS

The annual meeting of the Massachusetts Association of Medical Technologists will be held in the Hotel Somerset, Boston, April 24.

Among the speakers will be Drs. John Conlin, Wendell Caraway and Arnold Lear.

AMERICAN NEUROLOGICAL ASSOCIATION

The seventy-ninth annual meeting of the American Neurological Association will be held at the Hotel Claridge, Atlantic City, New Jersey, June 14–16.

SOCIETY FOR INVESTIGATIVE DERMATOLOGY

The fifteenth annual meeting of the Society for Investigative Dermatology will be held at the Clift, San Francisco, June 19 and 20. Room reservations must be made through the Convention Bureau, American Medical Association. Further information may be obtained from Dr. Herman Beerman, 255 South 17th Street, Philadelphia 3, Pennsylvania.

NATIONAL ASSOCIATION FOR THE PREVENTION OF TUBERCULOSIS

The fourth Commonwealth Health and Tuberculosis Conference will be held at the Royal Festival Hall, London, June 21 to 25, 1955. Further information may be obtained from the secretary-general, National Association for the Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W.C.1, England.

PAN AMERICAN CONGRESS OF OPHTHALMOLOGY

The third interim congress of the Pan American Association of Ophthalmology will be held in São Paulo, Brazil, June 17 to 21. Papers will be presented by physicians from North, Central and South America.

SOCIETY MEETINGS AND CONFERENCES

March 26–31. Consultation Clinics for Crippled Children. Page 303, issue of February 18.

March 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

March 28. National Gastroenterological Association. Page 265, issue of February 11.

March 31. Boston City Hospital Seminar on Peripheral Disease. Page 443, issue of March 11.

March 31. Tufts Medical Alumni Dinner Meeting. Page 443, issue of March 11.

March 31–April 2. American College of Surgeons. Sectional Meeting. Page 266, issue of February 11.

March 31–April 28. Consultation Clinics for Crippled Children. Page 490, issue of March 18.

April 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

April 7. Massachusetts Academy of General Practice. Page 443, issue of March 11.

April 8–11. International Academy of Proctology. Page 130, issue of January 21.

April 8 and 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.

April 9. New England Society of Anesthesiologists. Page 399, issue of March 4.

April 9–May 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

April 10. American Congress of Physical Medicine. Page 266, issue of February 11.

April 13. New York Society for Circulatory Diseases. Page 491, issue of March 18.

April 13. Harvard Medical Society. Page 539.

April 17 and May 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.

April 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

April 21–24. Seminar and Conference on Cancer Cytology. Page 346, issue of February 25.

April 24. Boston City Hospital Alumni Association. Page 491, issue of March 18.

April 24. Massachusetts Association of Medical Technologists. Notice above.

April 26–May 2. International College of Surgeons. Page 492, issue of March 18.

April 29 and 30. New York Academy of Medicine. Eastern States Health-Education Conference. Page 491, issue of March 18.

April 29, 30 and May 1. American Goiter Association. Hotel Somerset, Boston.

May 1. State University College of Medicine at New York City. Alumni Association. Page 400, issue of March 4.

May 10–12. Institute of Industrial Health. Page 491, issue of March 18.

May 11. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)

May 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.

May 12. New England Obstetrical and Gynecological Society. Spring Meeting. Longmeadow Country Club, Springfield.

May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

May 31–June 3. American Urological Association. Page xvii, issue of July 23.

June 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.

June 13–17. American Society of Medical Technologists. Page 444, issue of March 11.

June 14–16. American Neurological Association. Notice above.

June 15–18. Medical Library Association. Page 491, issue of March 18.

June 17–19. American Geriatrics Society. Page 266, issue of February 11.

June 17–21. Pan American Congress of Ophthalmology. Notice above.

June 19 and 20. Society for Investigative Dermatology. Notice above.

July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

July 23–29. International Cancer Congress. Page 914, issue of November 26.

July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

June 21–25, 1955. National Association for the Prevention of Tuberculosis. Notice above.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, APRIL 1

THURSDAY, APRIL 1

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. The Natural History of Hypertension. Dr. Alex M. Burgess. Regional Office of the Veterans Administration. Conference Room, 4th floor, 17 Court Street, Boston.

(*Notices concluded on page xix*)